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The
PHYSIOLOGICAL BASIS
of
MEDICAL PRACTICE

A UNIVERSITY OF TORONTO
TEXT IN APPLIED PHYSIOLOGY

By

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PREFACE TO FIRST EDITION

Physiology is a science in its own right and the laboratory worker who pursues his researches quite detached from medical problems need offer no apology for his academic outlook. Indeed some of the most valuable contributions to medical science have been the outcome of laboratory studies whose applications could not have been foreseen. Nevertheless, we feel that the teacher of physiology in a medical school owes it to his students, whose ultimate interest it must be conceded is in the diagnosis and treatment of disease, to emphasize those aspects of the subject which will throw light upon disorders of function. The physiologist can in this way play a part in giving the student and practitioner a vantage point from which he may gain a rational view of pathological processes.

We have endeavored to write a book which will serve to link the laboratory and the clinic, and which will therefore promote continuity of physiological teaching throughout the pre-clinical and clinical years of the under-graduate course. It is also hoped that when the principles underlying diseased states are pointed out to the medical student, and he is shown how a knowledge of such principles aids in the interpretation of symptoms or in directing treatment, he will take a keener interest in physiological studies. When such studies are restricted to the classical aspects of the subject, apparently remote from clinical application, the student is likely to regard them only as a task which his teachers in their inscrutable wisdom have condemned him to perform. Too often he gains the idea, from such a course, that physiology is of very limited utility and comes to believe that, having once passed into the clinical years, most of what he has "crammed" for examination purposes may be forgotten without detriment to his more purely medical studies. Unfortunately, he does not always realize at this stage in his education how great has been the part which physiological discoveries have played in the progress of medicine, and that the practice of today has evolved from the "theories" of yesterday.

Many physiological problems can be approached only through animal experimentation. Advances in many fields, most notably in those of carbohydrate metabolism, nutrition, and endocrinology, bear witness to the fertility of this method of research. On the other hand, many problems can be elucidated only by observations upon man, and physiology has gained much from clinical research. The normal human subject as an experimental animal possesses unique advantages for many types of investigation; and in disease, nature produces abnormalities of structure and function which the physiological laboratory can imitate only in the crudest way. Within recent years the clinical physiologist, fully realizing these advantages and the opportunities afforded by the hospital wards, has contributed very largely to physiological knowledge. In many instances, clinical research has not only revealed the true nature of the underlying process in disease, but has cast a light into some dark corner of physiology as well; several examples of clinical investigation which have pointed the way to the physiologist could be cited. In the last century, knowledge of the processes of disease was sought mainly in studies of morbid *anatomy*; biochemistry was in its infancy and many of the procedures now commonly employed for the investigation of the human subject had not been devised. Today, the student of scientific medicine is directing his attention more and more to the study of morbid *physiology* in his efforts to solve clinical problems. This newer outlook has borne fruit in many fields. It has had the beneficent result of drawing the clinic and the

physiological and biochemical laboratories onto common ground from which it has often been possible to launch a joint attack upon disease. We feel that this modern trend in the field of research should be reflected in the teaching of medical students, and have therefore given greater prominence to clinical aspects of the subject than is usual in physiological texts.

In order to understand the function of an organ it is usually essential to have a knowledge of its structure. For this reason we have followed the plan of preceding the account of the physiology of a part by a short description of its morphology and, in many instances, of its nerve and blood supply. The architecture and functions of the central nervous system are so intimately related that some space has been devoted to a description of the more important fiber tracts and grey masses of the cerebrum, cerebellum and spinal cord.

We wish to thank our colleagues in physiology, biochemistry and anatomy whom we have drawn upon on so many occasions for information and advice; without their generous help the undertaking would have been an almost impossible one. We are also deeply grateful for the unstinted assistance which we have received from our friends on the clinical staff, several of whom have read parts of the text in manuscript or in proof. We wish especially to acknowledge our indebtedness to Professor A. M. Wynne, who has written the section on the oxidizing systems of living cells, to Dr. J. K. W. Ferguson for his collaboration in the preparation of Chapter XXXIII, and to Professor C. B. Weld and Dr. E. T. Waters whose stimulating criticisms and sound counsel have been invaluable.

Finally, we wish to thank our secretaries, Miss Mabel Cory and Miss Dudley Martin, who have spent so many tedious hours in preparing the manuscript for the press, in checking the references and in compiling the index.

October 15, 1936

C. H. B.
N. B. T.

PREFACE TO THE FOURTH EDITION

This book, in its fourth edition, has taken on a new form and dress which the authors feel sure will be welcomed by the student. The two-column format has necessitated an entire resetting of type and along with this as much proof-reading, indexing and correcting as is required in a first edition—and incidentally, with little doubt, as many uncorrected errors. Besides saving space, the reader will find that the double-column page makes for much easier reading, more of the subject is before his eyes at the moment and his mind will be less distracted by the turning of pages. The majority of the figures have been reduced to one column width thus permitting a further saving of space, with little, if any, loss of clearness. A number of new figures have been added, others have been replaced or improved by re-drawing. There has been no abridgement of the text: new material in excess of deletions, has actually resulted in a considerable extension.

Dr. Wynne has rewritten his section entitled *Intracellular oxidation and the biological transformation of energy*. We cordially offer him our thanks. We also wish to thank again Miss Mabel Corey for her invaluable secretarial assistance.

C. H. B.

N. B. T.

October, 1945.



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SECTION I. THE BLOOD AND LYMPH

CHAPTER I

THE PHYSIOLOGICAL PROPERTIES, PHYSICAL CHARACTERS AND COMPOSITION OF THE BLOOD

OUTLINE OF THE FUNCTIONS OF BLOOD

In animals whose bodies are composed of many cells (the metazoa) the blood serves those purposes which, for unicellular organisms (the protozoa) are carried out by the fluid medium, the salt or fresh water, which surrounds them and bathes their surfaces. For instance, an organism such as the amoeba acquires oxygen by diffusion directly from the environment into the interior of the cell. Similarly the carbon dioxide diffuses outwards. The processes of nutrition and the excretion of the products of the cell's metabolism are accomplished in a manner equally simple. Food is taken in through the cell membrane either in solution or as particulate matter, and waste products pass into the surrounding medium. Other requirements of this organism, such as the maintenance of an optimum temperature and the proper degree of moisture, are dependent on the immediate environment.

The elemental needs of each cell in a multicellular form from the most primitive type to the highest vertebrate are the same as for the unicellular organism; yet in the evolution of the higher forms the cells composing their bodies have become farther and farther removed from immediate contact with the outside world. Myriads of cells have become packed together, and the deeper ones could not possibly satisfy their needs after the direct and simple fashion of the unicellular forms. The more primitive multicellular types overcame the difficulty by the development of canal systems which opened upon their exteriors and through which the ocean waters flowed freely in and out, bringing oxygen and aliment to the more deeply lying cell and bearing carbon dioxide and other excretory products away. This, the first attempt at a circulation, was an open one. As higher forms evolved the circulation became closed and the waters of the environment no longer flowed and ebbed through the body. No longer could the interchange of the respiratory gases and the absorption of nutriment be carried out in this direct and simple way. Yet the vessels of this closed circu-

latory system were filled with a fluid which took the place of and fulfilled the duties of the watery environment of the more primitive types. The blood and other body fluids may be looked upon as that environment which has become enclosed within the bodies of the higher forms, and has undergone certain modifications in its composition to meet the requirements of the more specialized cells which it bathes.

The similarity between the compositions of sea water and blood which has been stressed by the researches of Macallum lends support to these views on the evolution of the blood.¹ This brief account will also serve as an introduction to a consideration of the functions of the body fluids, since their duties are to satisfy in the same way as did their prototype, the requirements of the individual cells.

(1) *Respiratory.* The transport of oxygen from the air in the lungs to the tissues, and of carbon dioxide from the tissues to the lungs.

(2) *Nutritive.* The conveyance of food materials, glucose, amino acids and fats from the alimentary canal to the tissues.

(3) *Excretory.* The removal of waste products of metabolism, e.g., urea, uric acid, creatinine, etc.

(4) *The maintenance of the water content of the tissues.* Though the blood itself is contained within vascular channels a constant interchange of fluid through the vessel walls takes place. This fluid which has left the blood vessels and come into direct contact with the tissue cells is known as the lymph, or tissue juice. It closely resembles the blood fluid in chemical composition. Through the medium of the transuded fluid the final stage in the transportation of oxygen and food materials to the tissues and the first stage in the journey of CO₂ and waste products from the tissues are made. It is the very high solvent and ionizing powers of water of which the blood fluid and lymph are chiefly constituted (p. 2) which render these such admirable

¹ Sea water of today differs from blood serum in having a total salt concentration of about 3 per cent, a much higher concentration of magnesium and a lower concentration of potassium. But Macallum points out that the sea water of the geological period when the ancestors of mammalian forms adapted themselves to a terrestrial life was probably closely similar in its inorganic composition to blood serum.

media for the carrying out of the complex chemical processes of the body.²

(5) *To regulate body temperature.* The body owes its ability to regulate its temperature (p. 624) largely to the water of the blood and tissue fluids. Water possesses three qualities which fit it pre-eminently to fulfil this purpose.

(a) The *specific heat*³ of water is considerably higher than that of any other liquid or solid. On account of this great heat storage power of water, sudden changes of body temperature are avoided and even a cold-blooded animal such as the frog has, due to this purely physical quality, some ability to maintain a relatively constant body temperature against transient fluctuations in environmental temperature. A man of average weight develops 3000 Calories in 24 hours. This amount of heat is capable of raising the temperature of his tissues (which are mostly water) only about 32°C. Heat elimination (radiation, etc.) is able to keep pace with heat production and the body temperature varies but slightly within normal limits. But it has been pointed out by L. J. Henderson that if the tissues had the low heat storage capacity (spec. heat) of most substances, an amount of heat equal to 3000 Calories would raise the temperature of the tissues and fluids of the body by from 100°–150°C.

(b) *High conductivity.* The thermal conductivity of water is greater than that of any other ordinary liquid. The advantage of this in the dissipation of heat from deeply situated regions of the body is obvious.

(c) *High latent heat of evaporation.* More heat is required for the vaporization of water than for that of an equivalent amount of any other liquid. 1 cc. of water requires about 0.6 Calories (large) for its vaporization. This figure is 50 per cent higher than that of water's closest competitor. Fluid is being constantly lost from the body through evaporation from the lungs and skin. A large amount of heat is lost in the process (p. 623).

These physical properties of water which make it ideal as a heat regulating medium are enhanced by other purely *physiological factors*. The mobility of the blood, and the readiness with which it may be quickly redistributed in the body, combined with the unique physical properties of the fluid itself, render it so highly efficient as a regulator of body temperature. The blood may in a moment be brought from deeper to superficial regions and spread out in fine vessels over a broad area just beneath the skin, and in this way will greatly increase the radiation of heat. At another instant, in order that heat may be conserved, the fluid is drained from the surface areas and collected in

the deeper parts of the body—internal organs, muscles, etc.

(6) *Protective and regulatory.* The blood and lymph contain certain chemical substances of a complex nature, antitoxins, lysins, and other antibodies, which are the basis of the body's defence against injurious agents of various kinds. The circulating fluids are also the vehicle by which the hormones of the different ductless glands are brought into direct contact with the cells of the tissues.

THE COMPOSITION OF BLOOD

The blood is a highly complex fluid in which solid elements are suspended—the *corpuscles or blood cells*. Its specific gravity is from 1.050 to 1.060 and its viscosity from 5 to 6 times that of water. If blood is centrifuged before it has had time to clot, or if clotting is prevented by special means (p. 91), the solid elements are thrown down and separated from the fluid portion. The latter is called the *plasma* and contains *proteins*, as well as many organic and inorganic substances in solution—nutritive and excretory materials, antibodies and hormones, and other substances of an unknown or imperfectly known chemical constitution. The specific gravity of plasma is normally around 1.027 but varies with the protein concentration. The cells constitute about 45 per cent of the volume of human blood, the plasma 55 per cent. In the following table scheme are given the constituents of the blood, grouped upon a physiological basis.

Whole blood:

A. Cells:

- (1) Red corpuscles or erythrocytes
- (2) White corpuscles or leucocytes
- (3) Platelets or thrombocytes

B. Plasma:

- (1) *Water*, 91 to 92 per cent
- (2) *Solids*, 8 to 9 per cent
 - (a) *Proteins*, 7 per cent, Serum albumin, serum globulin and fibrinogen.⁴
 - (b) *Inorganic constituents*, 0.9 per cent. Sodium, calcium, potassium, magnesium, phosphorus, etc.
 - (c) *Organic constituents* (other than protein). Non-protein nitrogenous substances, (urea, uric acid, xanthine, hypoxanthine, creatine and creatinine, ammonia and amino acids) neutral fats, phospholipids, cholesterol, glucose.
 - (d) *Internal secretions, antibodies and various enzymes, amylases, proteases, lipases, esterases, etc.*

² The dielectric constant of water upon which the ionization of substances in aqueous solution depends is higher than that of any other liquid.

³ The specific heat of a substance is defined as the number of calories required to raise 1 gram of the substance one degree Centigrade.

⁴ Plasma from which the fibrinogen has been removed through clotting (p. 88) is spoken of as serum.

INORGANIC CONSTITUENTS

The concentration of the plasma in the various inorganic materials is given in table 1.

It will be noted that the plasma is relatively rich in sodium and calcium but poor in potassium and magnesium whereas in the cells conditions are reversed, these showing a relatively high concentration in potassium and magnesium but being lacking in sodium and calcium. The iron is confined almost exclusively to the red cells and most of it is in the hemoglobin molecule. A very small proportion of the iron of the cells, however, is in some other form. It has been suggested that this is bound loosely with the lecithin of the cell stroma (p. 7).

40 mgm. per 100 cc. and the greater proportion of this is in the cells.

The inorganic and ester fractions are extracted from blood by the precipitation of the proteins with trichloroacetic acid and filtering. The phosphorus contained in the filtrate is spoken of as the acid soluble phosphorus. Upon extraction of blood with alcohol-ether the lipid phosphorus is obtained. The phosphorus of blood is therefore separable into two classes.

- (1) *The acid soluble which includes*
(a) Inorganic phosphorus
(b) Ester phosphorus
(2) *Alcohol-ether soluble, i.e.,*
lipid phosphorus.

}

organic phosphorus

The ester, or organic acid-soluble phosphorus is obtained by determining the total acid soluble P and subtracting from it the inorganic phosphorus. Of the

TABLE 1
Inorganic constituents of plasma, red cells and whole blood, milligrams per 100 cc. average values

	SODIUM	POTASSIUM	CALCIUM	MAGNESIUM	CHLORINE	IODINE	IRON	COPPER	TOTAL BASE CC. N/10 NaOH
Plasma.....	340	20	10	2.7	370		0.1		160
Cells.....	0	420	0	6.0	190		100.0		
Whole blood.....	160	200	5	4.0	250	0.01	45.0	0.1	

The concentrations of these various inorganic constituents are also commonly expressed as milli-equivalents (m.equ.) per liter. Thus serum contains 100 mgm. of calcium per liter. The molecular weight of Ca is 40.07. So being divalent its milli-equivalent is 20.03. The concentration of calcium in serum is therefore $\frac{100}{20.03} = 4.9$ milli-equivalents per liter. Sodium is monovalent and has a molecular weight of 23; serum therefore contains $\frac{3400}{23} = 147.8$ m.equ. per liter.

Phosphorus

Four phosphorus compounds exist in blood. One of these is *inorganic phosphorus* (orthophosphate). The three other phosphorus fractions are in *organic* combination and are as follows.

- a. *Ester phosphorus*, e.g., diphosphoglycerate, adenosinetriphosphate, hexose phosphates, glycerophosphate.
- b. *Lipid phosphorus*, e.g., the phosphatides lecithin, cephalin, sphingomyelin.
- c. *Nucleic acid phosphorus*.

According to Kay the nucleic acid phosphorus in normal human blood is negligible. It is derived from the nuclei of white cells and the reticulum of the reticulocytes. In abnormal blood containing a large number of leucocytes, reticulocytes or nucleated red cells this fraction may however constitute a considerable proportion of the total phosphorus.

The inorganic phosphorus (3 mgm. per 100 cc.) is according to most observers about equally distributed between cells and plasma. The quantity of organic phosphorus in blood is many times greater than the inorganic. In whole blood it amounts to from 35 to

ester phosphorus, all of which is intracellular, about one-quarter is hydrolyzable by bone phosphatase (p. 716). The hydrolyzable portion is mainly adenosinetriphosphate, and the non-hydrolyzable part mainly diphosphoglycerate. Since the nucleic acid phosphorus is negligible in normal blood, the acid soluble + the alcohol-ether soluble phosphorus equals the total phosphorus as determined by wet-ashing.

In the following table is given the distribution of inorganic, ester and lipid phosphorus in normal blood.

Phosphorus in whole blood
Milligrams per 100 cc., average figures

1. Total Phosphorus..... 40
2. Total acid soluble—90 per cent in cells..... 27
3. Inorganic—in cells and plasma..... 3*
4. Ester (2—3)—practically all in cells..... 24
5. Lipid (1—2)—in cells and plasma..... 13

* In infants and young children, the inorganic phosphorus is from 1 to 3 mgm. per cent higher than it is in adults.

The phosphorus compounds of the blood and tissues play an important rôle in maintaining the electrolyte equilibrium within the red cells and in regulating the

acid base balance. Diabetic acidosis, for example, and the acidosis induced by the ingestion of ammonium chloride, are accompanied by increased excretion of phosphorus in the urine and a pronounced reduction of the organic acid-soluble phosphorus in the blood cells. Reverse changes occur in alkalosis; the reduction in the chloride of the blood following pyloric obstruction, and the alkalosis caused by over-breathing are associated with a reduction in the urinary excretion of phosphates and an increase in the inorganic and ester phosphorus of the blood. In renal insufficiency, the inorganic phosphorus in the plasma and cells and the ester phosphorus (diphosphoglycerate) in the cells are greatly increased. The inorganic and ester phosphorus are reduced in rickets but a rapid increase accompanies the healing process. The inorganic phosphorus is diminished after the injection of insulin and in hyperparathyroidism (p. 708). In anemias associated with high reticulocyte counts and in leukemia, the concentration of ester phosphorus in the blood is increased. The inorganic phosphorus is increased in some forms of tetany.

ORGANIC CONSTITUENTS

Plasma proteins

The concentration of total protein in the plasma and the proportions of the three fractions vary from species to species but under ordinary conditions of health remain relatively constant between individuals of the same species.

The values for human plasma of total protein and of the different fractions are given in the table below.

Protein in human plasma

Grams per 100 cc., average values

Total Protein.....	7.1
Fibrinogen.....	0.27
Serum globulin.....	2.7
Serum albumin.....	4.1
Ratio of three fractions (approximately).....	1-10-15
Alb./Globulin ratio.....	1.51

Serum globulin can be separated into two fractions—*euglobulin* and *pseudoglobulin*—by 1.0 molar sodium sulphate, which precipitates the former. Fibrinogen has been isolated and prepared in crystalline form. X-ray diffraction studies indicate that its molecule is structurally similar to such fibrous proteins as collagen and myosin (see p. 538). The molecular weights of the plasma proteins are given in Chapter XLVII.

In some animals the globulin is equal to or exceeds the albumin. Of the three fractions fibrinogen is always in lowest concentration and it is considerably

lower in human plasma than in that of some animals (e.g., 0.58, 0.72, 0.60 gram per 100 cc. in dog, cow and goat respectively).

as physiological

PATHOLOGICAL VARIATIONS IN CONCENTRATION. A rise in the fibrinogen and globulin fractions occurs in pulmonary tuberculosis, pneumonia, septic infections and pregnancy. A relative increase in total plasma protein results from a reduction in the water of the plasma (an hydremia, p. 19). The fibrinogen is increased in tissue injury of various sorts and in parathyroid overdosage. It is markedly reduced in animals by liver damage, occlusion of the hepatic vessels, after hepatectomy and in various clinical conditions involving the liver, e.g. phosphorus poisoning, acute yellow atrophy, etc. The concentration of *total* protein is reduced after hemorrhage (since the blood volume is for a time made good by the passage of a saline fluid from the tissues into the vessels), in nephritis, as a result of malnutrition, during pregnancy and lactation and in parenchymatous liver disease. After hemorrhage, the regeneration of fibrinogen occurs more rapidly than that of the other proteins. Globulin is regenerated more rapidly than is albumin. The regeneration of all three fractions, but especially of the albumin, is favored by a high protein diet. In nephritis and in malnutrition the low concentration of total protein is due chiefly to a reduction in the albumin fraction (p. 405). The globulin depletion is less pronounced so that the albumin-globulin ratio is lowered. The fibrinogen concentration is little affected.

ORIGIN. In the *embryo*, the mesenchyme cells through a process of secretion or by the actual solution of their substance furnish the fluid (embryonic plasma) which floats the primitive blood cells (p. 77). The albumin fraction is formed earlier than the other proteins which do not appear in the plasma of the chick embryo until after the 14th day of incubation.

In the *adult*, five possible sources of the plasma proteins have been suggested—namely, disintegrating blood cells (red or white), the general tissue cells, reticuloendothelial cells of spleen, bone marrow, etc., and the liver. We do not know with certainty the origin of the albumin and globulin fractions, though it is more than probable that they are produced in the liver, for they undergo a pronounced reduction in conditions which interfere with hepatic function. The evidence points definitely to the liver as the site of fibrinogen production since as mentioned above

the concentration of this fraction is reduced by liver damage or hepatectomy. When the liver returns to a healthy state after injury has been induced by an agent such as phosphorus or chloroform, the fibrinogen level also returns to normal. Following slight liver injury or during the repair of a hepatic lesion, which might be expected to stimulate the functional activity of the organ, the fibrinogen may be actually higher than normal.

FUNCTIONS. (1) Fibrinogen is essential for the clotting of the blood (p. 88).

(2) All three proteins serve to maintain the osmotic pressure (p. 23) of the blood. The large

that of albumin. In equivalent concentrations, serum albumin has an osmotic activity 2.4 times that of serum globulin (Keys).

(3) *Viscosity.* The proteins give a certain viscosity to the blood which is a factor in the maintenance of the normal blood pressure (p. 122).

(4) They aid in the regulation of the acid-base balance of the blood (p. 106).

(5) *Stability of the blood* (see p. 50). The globulin and fibrinogen fractions influence the tendency of the corpuscles to adhere to one another and form rouleaux or clumps.

(6) *Trephones.* Carrel has shown that the leucocytes prepare substances from the plasma

TABLE 2*

The nitrogen partition in the blood of normal individuals and the distribution of the various nitrogenous constituents between the cells and serum

	CORPUSCLES			PLASMA			WHOLE BLOOD		
	Maxi- mum	Mini- mum	Average	Maxi- mum	Mini- mum	Average	Maxi- mum	Mini- mum	Average
	mg. per 100 cc.	mg. per 100 cc.	mg. per 100 cc.	mg. per 100 cc.	mg. per 100 cc.	mg. per 100 cc.	mg. per 100 cc.	mg. per 100 cc.	mg. per 100 cc.
(a) Taken from Wu:									
Total non-protein nitrogen.....	61	39	49	36	20	29			
Urea N.....	22	12	17	23	13	19			
Amino-acid N.....	11	8	10	8	5	6			
Uric acid.....	4	1	2	5	2	4			
Creatine.....	8	4	6	0	0	0			
Creatinine.....	3	1.6	2.5	1.5	1	1.2			
Undetermined N.....			19			2.1			
(b) Taken from Berglund:									
Total non-protein nitrogen.....	55	38	44	30	18	25	39	28	32
Urea N.....	13	8	10	17	10	12	15	9	12
Amino-acid.....	11	7	8	6	4	5	8	6	6
Undetermined N.....	34	18	25	12	2	7	18	10	14

* Reprinted from Peters and Van Slyke, *Quantitative Clinical Chemistry*, vol. I, p. 267.

molecules of the proteins do not pass readily through the normal capillary membrane. The osmotic pressure which they exert amounts to, in man, between 25 and 30 mm. Hg. The pressure which each fraction exerts is inversely related to the size of its molecule and directly related to its concentration in the plasma. The molecular weight of fibrinogen is over 200,000 and its concentration is low; it therefore contributes little toward the total osmotic pressure. Albumin is in the highest concentration and its molecule has the least weight (70,000-75,000). The osmotic pressure of the plasma, therefore, depends largely upon this fraction. The molecular weight of serum globulin is between 150,000 and 190,000 and its concentration is considerably less than

proteins which are essential for the nourishment of tissue cells grown in cultures. These substances he has termed trephones (p. 74).

(7) *Immune substances* are associated with the globulin fraction which is increased during the process of immunization. They appear to be attached to the globulin molecule.

(8) They serve as a reserve of protein upon which the body draws during fasting or when the protein intake is inadequate.

Plasmapheresis. The importance of the plasma proteins is demonstrated by this procedure which consists in bleeding an animal and returning the red cells suspended in Locke's solution to the body. "Shock" results, followed by death when the total protein is reduced to between 1 and 2 per cent. No

ill effects result however if the cells are suspended in serum before they are re-introduced. When depletion of the proteins is not carried to the point where fatal shock ensues, a marked rise in protein concentration occurs within 15 minutes which indicates that during this time a store of preformed protein is drawn upon for the replacement of the protein which has been removed. The regeneration is slower after this though fairly rapid for the first 24 hours. It becomes progressively slower during succeeding days. The proteins are restored to the normal level in from 2 to 7 days, provided that the diet contains a sufficiency of high quality protein.

The non-protein nitrogen (N.P.N.) or non-coagulable nitrogen of blood

By the term non-protein-nitrogen is meant the nitrogen of those substances e.g. urea, uric acid creatinine, etc., listed on page 5. They may be extracted from blood or plasma by treating either of these with a reagent, such as trichloroacetic acid, which precipitates the proteins, filtering and determining the nitrogen in the filtrate. These substances are in part absorbed with, or derived from the food, and in part are the waste products of tissue catabolism. The total N.P.N. of whole blood amounts to from 28 to 40 mgms. per 100 cc. It constitutes from 1 to 2 per cent of the total nitrogen of the blood. Its concentration in the cells is nearly double that in the plasma. The proportions of the different constituents are given in table 2.

The term undetermined nitrogen embraces the nitrogen of ammonia, purines, and other non-protein substances of unknown nature.

PATHOLOGICAL VARIATIONS IN N.P.N. The N.P.N. at any given level represents the balance struck between the quantity of nitrogenous waste products entering the blood and the quantity excreted in the urine. In renal insufficiency therefore, the non-protein nitrogen is elevated, and in certain cases may be ten times the normal. On the other hand, a rise in the N.P.N. occurs in conditions, such as fevers, which are associated with excessive tissue catabolism. In the later months of pregnancy the N.P.N. is reduced. The reduction has been attributed to the diversion of nitrogen to the growing fetus and the reduction of protein catabolism in the maternal tissues.

The following is a list of the chief conditions associated with an elevation of the N.P.N. of the blood.

- Adrenal insufficiency
- Dehydration
- Haemorrhage into the gastrointestinal tract
- Infectious fevers, lobar pneumonia
- Intestinal obstruction
- Parathyroid intoxication (in animals)
- Peritonitis
- Renal insufficiency

Cholesterol (see chapter LI, and p. 649)

CHAPTER II

THE RED CELLS OR ERYTHROCYTES

THE SIZE, SHAPE AND STRUCTURE OF THE RED CELL

Human erythrocytes are disc-shaped, non-nucleated elements having a mean diameter of 7.2 microns (0.0072 mm.) and a thickness of about 2.2 microns. As a result of osmotic changes¹ the diameter increases with a shift in the acid-base balance of the blood toward the acid side. The cell is therefore slightly larger in venous than in arterial blood; its diameter is increased by about 0.5 μ in muscular exercise and reduced by forced breathing. The central portion of the cell is much thinner than its edges, which appear heaped up into a circumferential mound around a central depression. This construction gives it a biconcave contour or a roughly dumb-bell outline when viewed edgewise (figs. 1 and 2).² The average area of a red cell is 120 square microns and the volume 85 cu. microns. The mature erythrocyte can scarcely be considered a living cell in the ordinary sense, since it possesses no nucleus and does not consume an appreciable amount of oxygen. Young (nucleated or reticulated) cells, on the other hand, and the nucleated cells of

¹ These are the average dimensions of the cell measured in dry films. In the fresh state the diameter is larger by about 0.8 microns. There is considerable variation between the diameter of the smallest and largest cells found in a sample of normal blood. The range for dried films is shown in figure 2.

² Hartridge has pointed out the advantage of this design for the transport of oxygen. Of all geometrical figures the sphere is the one in which its centre is equidistant from all points upon its surface. The adoption of this form by the red cell would therefore have ensured the diffusion of oxygen to all parts of its interior at equal rates. But a sphere has the disadvantage of possessing the smallest surface in relation to its mass. A thin disc, on the other hand, presents an almost maximal surface area in relation to its bulk, yet in such a shape all parts on the surface are not equally distant from its center; the ends are further removed than the sides. The shape of the red cell—a thin disc with elevated rounded edges—is a compromise between these two forms. It secures the advantages of equal and rapid diffusion of oxygen to its interior and a relatively large surface area for the absorption of the gas.

The biconcave form also gives the red cell a mechanical advantage, in that the changes in volume which the cell undergoes from time to time are enabled to be effected with a minimal amount of tension being placed upon the cell membrane. The membrane covering the concavity of the cell moves freely out or in "like the bottom of an oil-can" as the cell increases or diminishes in volume.

lower vertebrates consume a considerable quantity of oxygen.

The red cell is bounded by a membrane made of protein in association with the lipid materials, lecithin and cholesterol. Though this membrane has not been demonstrated histologically, indirect evidence indicates its presence and suggests that it consists of an outer and inner layer of protein, each probably only a few molecules thick and enclosing between them three or four layers of lipid. It behaves as a semipermeable membrane. The body of the cell possesses a sponge-like *stroma* made of the same or similar materials probably in the form of a gel. The protein is a paraglobulin, small quantities of nucleoprotein are also present. In the meshes of the stroma, or more likely actually bound up in the stroma substance itself, the respiratory pigment *hemoglobin* is held. The fact that mechanical division of the cell, even into the finest particles fails to liberate the hemoglobin, supports the conception of a very intimate association of the pigment with the cell stroma. The water content of the cell is lower than that of most cells of the fixed tissues, amounting to about 60 per cent. Hemoglobin makes up from 80 to 90 per cent of the total solids of the cell (and about 34 per cent of its fresh weight). Other proteins (0.5 to 1 per cent) phospholipids (lecithin and cephalin) and cholesterol (0.4 and 0.3 per cent respectively), inorganic salts (fig. 3), urea, amino acids, creatine, etc. make up the remainder of the cell solids. Potassium is the principle base in the human erythrocyte, and sodium in the red cells of the cat and dog. The specific gravity of the red cell is 1.091.

When a drop of freshly drawn normal blood is placed on a glass slide and examined under the microscope, many of the erythrocytes are seen to group themselves together with their broad surfaces in contact, like a pile of coins. This arrangement of the cells is spoken of as *rouleaux*. The blood loses the property of *rouleaux* formation a few hours after it has been shed, or if the cells, as in acholuric jaundice (p. 61) tend towards a globular form. An exaggerated tendency to the formation of *rouleaux* is seen in certain states and leads to an increase in the sedimentation rate of the blood cells (p. 50).

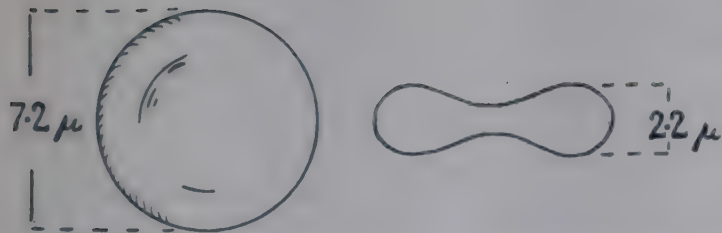


FIG. 1. Diagram showing dimensions of the red cell.

of the extra cells occurs within the first ten days, but for a few days the red cell count shows a progressive fall; for some weeks after this the count remains considerably above that of the adult. The total number of red cells in the body estimated upon the basis of 5 million per cubic millimeter is about thirty-five million million (35,000,000,000,000).

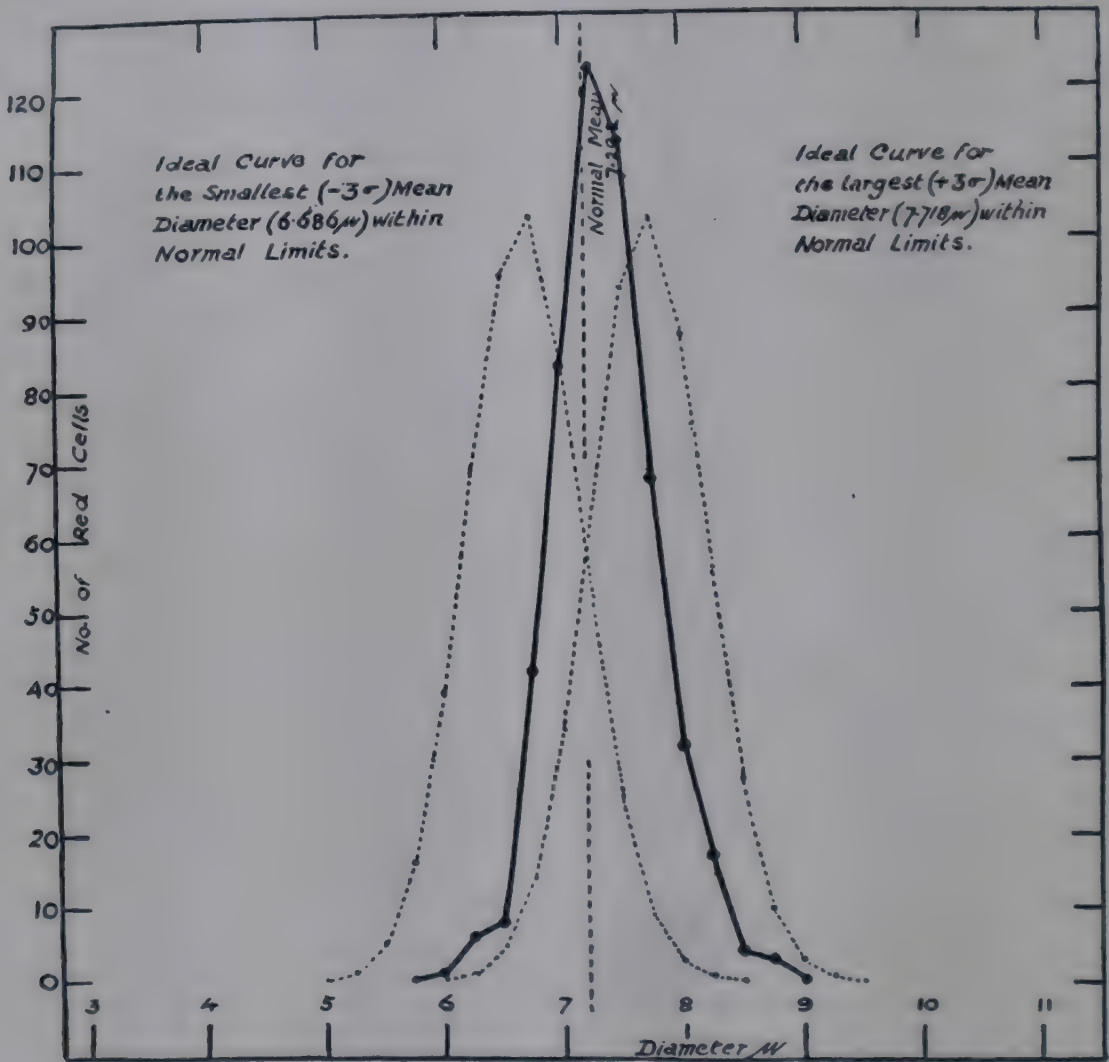


FIG. 2. Red-cell-diameter distribution curve for healthy men (after Price-Jones).

NUMBER

The average number of red cells in man is usually given as 5,000,000 per cubic millimeter for males, and 4,500,000 for females. The normal values are somewhat higher than the foregoing and 6,000,000 is not a very unusual figure for a robust male subject. Slight variations in the number of red cells, amounting to about 5 per cent, occur throughout the twenty-four hours. The count is lowest during sleep, becomes elevated after arising and increases gradually throughout the waking hours. At birth and in infancy the red cells are somewhat more numerous than in later life, but the earlier figures of 7 and 8 millions for the newborn child have not been confirmed by later work. Destruction of a large proportion

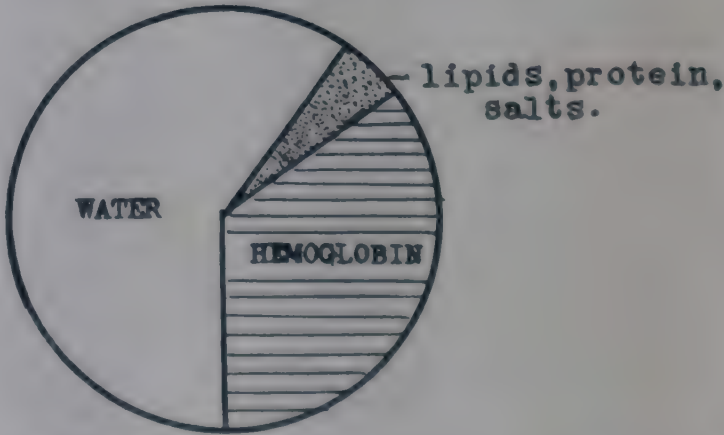


FIG. 3. Diagram showing composition of the red cell.

PHYSIOLOGICAL VARIATIONS IN THE NUMBER OF RED CELLS

Increase in the number of red cells occurs under the following conditions:

(a) HIGH ALTITUDES. It was first shown by Viault in 1889 that the inhabitants of mountainous regions, especially where the elevation above the sea is 10,000 feet or more, have constantly a much higher red cell count than persons living at sea level. The natives of some regions in the Peruvian Andes, where the altitude is 14,000 feet or more, have a red cell count 30 per cent above the normal (over 7 million per cubic millimeter). Not only the natives, but travellers sojourning even for a short time at these altitudes undergo an increase in the number of their red cells. The corpuscular increase is directly proportional to the altitude, as may be seen from table 3.

It is perhaps necessary to point out here that an increase or a decrease in the red cell count does not of itself inform one of an increase or decrease in the red cells of the body as a whole. The red cell count gives only an estimate of the *number of cells per unit quantity of blood* (p. 14). A reduction in the amount of plasma or of the water of the blood, for instance, would cause the *proportion* of red cells in the specimen to be increased. The increase in the red cells at high altitudes is, however, not simply due to loss of fluid and a greater concentration of the blood, for estimations of the total volume of blood in the body (see p. 16) prove that there is an *absolute* increase in the number of circulating cells. How is the increase brought about? Since a rise in the red cell count occurs so very soon after a person has been exposed to the rarefied atmosphere, the possibility is at once suggested that the red cells, under ordinary circumstances, are packed away from the general circulation—in a storehouse of some kind—but are quickly mobilized upon demand. When the functions of the spleen are considered (p. 53) it will be seen that this organ serves as a reservoir for red cells and is responsible for the sudden increase in their number which occurs early in the process of acclimatization to high altitudes.

The *permanent* and great elevation of the red cell count, which is a characteristic feature of the blood of natives and other persons after acclimatization to the rarefied atmosphere, cannot be explained in the same manner, for the number of cells which the spleen can put into circulation is limited. Under these circumstances there is, actually, an increased manufacture of erythrocytes by the blood-forming organ—the bone marrow. The cells which are formed by the over-stimulated marrow are discharged into the general circulation at a somewhat immature stage of their development. They are spoken of

as *reticulated cells* or *reticulocytes* since their protoplasm shows a delicate filigree or reticulum which stains with basic dyes (fig. 4 and p. 12). The ultimate cause of the corpuscular increase (polycythemia) is undoubtedly the lowered oxygen

TABLE 3

ALTITUDE IN THOUSANDS OF FEET	CORPUSCLES MILLIONS PER CUBIC MILLIMETER
0.7	4.5
4.4	5.2
8.0	6.0
10.0	6.6
12.0	6.8
12.4	6.8
13.3	7.5
15.6	7.8
16.9	7.6
18.2	8.3

From Barcroft after Hingston. In this table the altitude (in thousands of feet) multiplied by 0.225 gives a figure which approximates the increase in red cell count (in millions per cubic millimeter) above that at sea level. In this instance the count at sea level was 4.25 millions.

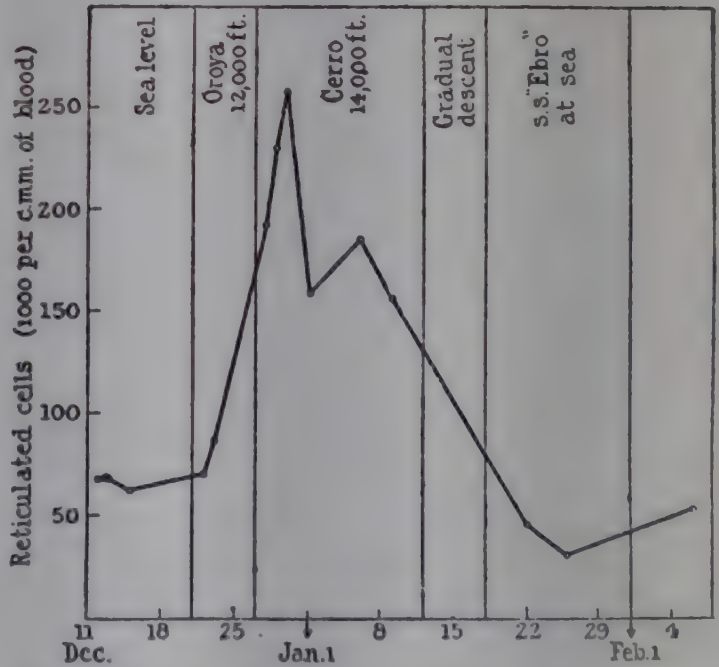


FIG. 4. Showing reticulocyte response to altitude (after Barcroft).

tension of the atmosphere, and consequently of the blood, since animals placed in an hermetically sealed cabinet and subjected to lowered oxygen tensions exhibit similar blood changes.

(b) MUSCULAR EXERCISE and certain EMOTIONAL STATES cause a temporary increase in the number of red cells as a result of an outpouring of concentrated blood from the spleen. This

may be looked upon as an emergency measure and, like that which occurs at high altitudes, is the response of the body to the tissues' call for oxygen.

(c) HEIGHTENED ENVIRONMENTAL temperature also causes a liberation of red cells from the splenic reservoir.

(d) Other conditions which tend to lower the oxygen tension of the arterial blood cause a rise in the number of circulating red cells. As in the response at high altitudes two factors are concerned, e.g., a discharge of blood from the spleen and a greater production of cells by the bone marrow.

Reduction in the number of red cells occurs at high barometric pressures, e.g., when the oxygen tension of the blood is higher than the normal. Animals, for example, living in deep mines have a lower red cell count than those at sea level.

ALTERATIONS IN THE NUMBER OF RED CELLS IN PATHOLOGICAL STATES

Increase in the number of red cells—polycythemia

Increase in the total number of red cells occurs as a compensatory measure in several pathological conditions and then apparently represents the response of the bone marrow to low oxygen tensions in the arterial blood. A red cell concentration of 7 million or more per cubic millimeter of blood is not unusual in the following conditions.

(a) EMPHYSEMA (p. 368) and other chronic diseases which interfere with the oxygenation of the blood in the lungs (anoxia), e.g., tracheal stenosis, pneumothorax, tumor of the lung and pulmonary tuberculosis.

(b) CONGENITAL HEART DISEASE (p. 371).

(c) AYERZA'S DISEASE, a condition associated with dilatation and marked hypertrophy of the right heart, sclerosis of the pulmonary arteries and their branches with consequent obstruction of the blood-flow through the lungs. There is extreme cyanosis; emphysema, dyspnea and attacks of asthma are common accompaniments.

(d) CHRONIC CARBON MONOXIDE POISONING.

(e) CHEMICALS, e.g., chronic poisoning with arsenic, phosphorus and manganese, gum shellac, and certain aniline dyes.

(f) REPEATED SMALL HEMORRHAGES, the polycythemia then represents an overresponse of the bone marrow to the successive blood losses.

POLYCYTHEMIA VERA (synonyms, erythremia, splenomegalic polycythemia, Vasquez-Osler disease). Unlike the preceding types the polycythemia is not secondary to any known pathological condition. The disease appears to be

primarily centered in the red bone marrow which is greatly increased in amount and hyperplastic, extending into the shafts of the bones to displace the fatty marrow, and packed with normoblasts and mature erythrocytes. Megaloblasts are absent or very scarce. The number of red cells in the circulating blood may be as high as 14 million per cubic millimeter and a count as high as 20 million has been reported. The total blood volume is greatly increased. The viscosity of the blood is of course greatly elevated (p. 122). The concentration of hemoglobin in the individual cells and the chemical and physiological properties of the pigment are normal. The size, shape and general features of the red cells as a rule show nothing unusual and the number of reticulocytes is not greatly increased.

The chief features shown by the disease apart from those of the blood itself are cyanosis (p. 372), dyspnea on exertion, enlargement of the spleen, hemorrhages and a familial tendency. Death may occur from thrombosis of the portal vein or a cerebral vessel. The circulation rate (p. 224) is slowed and the diffusion rates of oxygen and CO_2 (p. 316) through the pulmonary epithelium are reduced, though during rest the oxygen saturation of the arterial blood is usually normal. The oxygen saturation of the blood is reduced, however, during exercise. Owing to the great increase in hemoglobin concentration the actual quantity of oxygen in the blood is greater than normal. If the polycythemia were a compensatory reaction brought about by the lowered rate of diffusion of oxygen through the pulmonary epithelium, one would expect that breathing air with a high pressure of oxygen would be of benefit, but this is not the case. Exposure, in a chamber, to a high oxygen tension for several days does not effect a reduction in the number of red cells. The reduced circulation rate may result in some way from the fact that the blood contains such a large load of oxygen that the tissues can obtain their quota from a smaller quantity of blood than normally. On the other hand, the reduced circulation rate may be due primarily to vasoconstriction in some part of the circulation. Some believe that narrowing of the caliber of the vessels of the bone marrow and the resulting low oxygen tension produced thereby provide the stimulus for the overproduction of blood cells. Studies of blood lactic acid concentration in polycythemia vera following muscular exercise lend support to the idea that a sluggish blood flow through the tissues is a causative factor. In normal persons and in the secondary types of polycythemia mentioned above, a rise in blood lactate occurs, whereas in polycythemia vera exercise causes a fall. This anomaly could be explained upon the basis of a high resting blood lactate as a result of a slow blood flow and the accumulation of lactic acid in the ischemic tissues.

Exercise would then, by causing vasodilatation, especially in the contracting muscles, tend to reduce the concentration of the metabolite in the blood. That this is the probable explanation is indicated by the observation that vasodilatation induced by heat also causes a fall in blood lactate in this disease. The phenomenon appears to be of fundamental significance, and not simply the result of the high erythrocyte concentration, because it is not abolished when the red cell count is brought down to normal by treatment with *phenylhydrazine hydrochloride*, a drug commonly employed in controlling the disease. Polycythemia can be produced in dogs by the daily administration of cobaltous chloride (8 mgm. daily for 2 or 3 weeks). The high red cell count thus induced is reduced to normal by feeding with whole beef or hog liver or by the daily injection of ascorbic acid. The effect of liver suggests the presence of an hepatic hormone possessing a depressant action upon bone marrow activity.

Reduction in the number of red cells below the normal is known as anemia. The causes and varieties of anemia are manifold and will be considered in chapter IX.

An *apparent decrease or increase* in the number of red cells occurs under certain conditions which upset the water balance of the body. It has already been pointed out that the red cell count gives merely an estimate of the proportion of cells to plasma. There may, for instance, be undue retention of water in the body, and the plasma or its watery constituents may then be increased (hydremia or hemodilution). The blood is diluted, and the number of red cells per unit of blood is reduced, yet there is no absolute decrease in the number of circulating cells. Conversely, a loss of plasma or of merely the water of the blood (anhydremia or hemoconcentration) will increase the red cell count, i.e., the blood becomes more concentrated though the total number of red cells in the body is not altered. Therefore in conditions associated with extreme dehydration (p. 17) of the body the number of red cells per unit of blood is increased.

A practical point to be remembered with regard to the estimation of the red cells is that their number may be relatively increased or decreased by purely *local* alterations in blood concentration. Pronounced dilatation of the capillaries of the region of skin from which the sample has been taken will cause a local slowing of the blood stream and congestion of the part. The loss of fluid from the vessel into the tissues and the clumping of corpuscles which may result from the greater capillary pressure will give a false estimate of the number of red cells. On the other hand, pressure

made upon the part by the examiner in order to hasten the flow of blood from a skin-puncture may express fluid from the tissues which will dilute the red cells in the specimen.

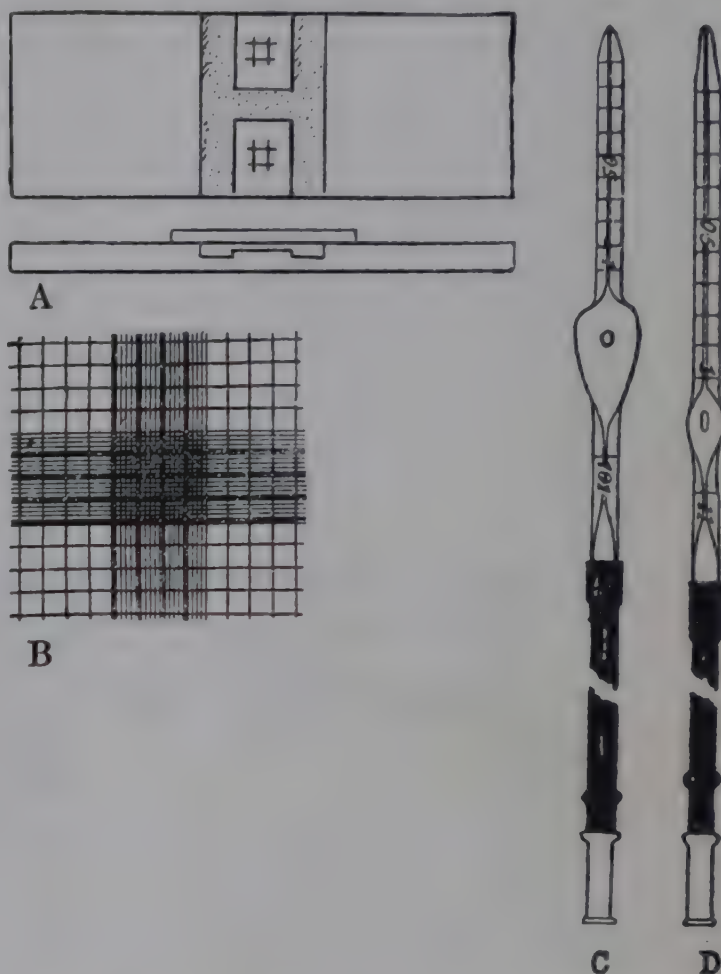


FIG. 5. Hemocytometer. A. Counting-slide shown on the flat and in cross section; it consists of two platforms surrounded on three sides by a trench; scale is engraved in the center of each platform. B, scale enlarged; C, pipette for diluting the blood 1 in 200, in counting of red cells; D, pipette for diluting the blood 1 in 20, in counting of white cells.

A drop of blood after dilution with a solution of 0.9 per cent sodium chloride is placed upon each of the glass platforms and a specially made cover glass gently applied. The space, filled with the diluted blood, between the surface of the platforms and the cover glass is $\frac{1}{10}$ mm. The scale is marked off in squares $\frac{1}{16}$ sq. mm. in area. Larger squares, each containing sixteen of the smaller squares, are marked off by heavier lines. The red cells in four large squares (on each platform) are counted under the low power of the microscope. The total number of cells is divided by one hundred and twenty-eight ($16 \times 4 \times 2$) which gives the average number in one small square. Now, the depth of the fluid is $\frac{1}{10}$ mm., so the volume upon each small square is $\frac{1}{16} \times \frac{1}{10} = \frac{1}{160}$ cu. mm. If the average number of red cells in each square is 6, then since the dilution was 1 in 200, the number per cu. mm. of blood is $6 \times 4000 \times 200 = 4,800,000$. The method of counting the white cells is similar in principle; but the blood is diluted 1 in 20 with a fluid which destroys the red cells and stains the white cells.

Estimation of red cells. An estimate of the concentration of red (or white) cells may be obtained by counting them directly after suitable dilution beneath the microscope, as in the method of Thoma-Zeiss.

The instrument used for this purpose is called a *hematocrit*. The reader is referred to texts on laboratory methods for details (see also fig. 5). Another method is by means of the *hematocrit* (fig. 6). In this the plasma and corpuscles are separated from one another by centrifugal force. The blood, rendered non-coagulable, is drawn into a graduated capillary tube, placed in a centrifuge and revolved at a speed of 3000 revolutions per second for 30 minutes. At the end of this time the original blood will be found to have separated into a clear colorless column of plasma and a red column—the corpuscles. The lengths of the two columns are read off by means of the graduations on the tube. The normal proportions of plasma and corpuscles in human blood are 55 and 45 respectively. That is, the volume of cells (packed cell volume) is 45 per cent of the total volume of the specimen of blood.

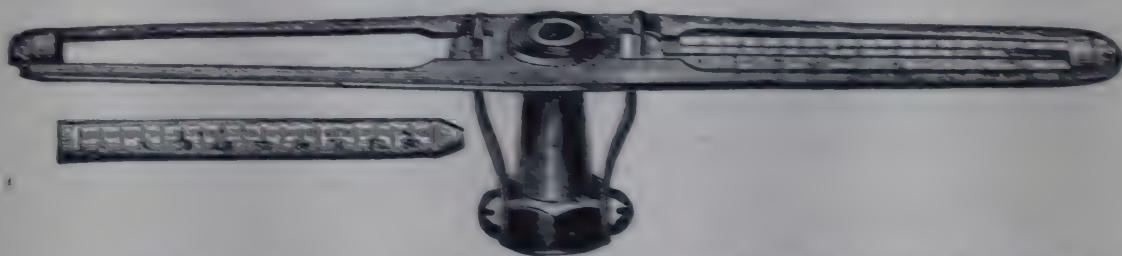


FIG. 6. Hematocrit (Daland). The graduated glass tubes are filled with blood and placed in the carrier which is then rotated on a centrifuge (see text).

VARIATIONS IN SIZE, SHAPE AND STRUCTURE OF THE RED CELLS

Under physiological conditions little change in shape of the red cell occurs, though a few fragmented cells may be found in normal blood. These are, as will be seen later (p. 56), simply remnants of senile cells which have undergone a natural disintegration in the blood stream. A slight change in volume, about 7.5 per cent occurs, due to osmotic changes incident to the respiratory cycle (p. 340). The red cells at birth and in early infancy are larger than in adult life. This as well as the higher cell count is responsible for the high packed cell volume (54 per cent) of the infant's blood.

In disease the red cell is subject to many changes in size, shape and structure. The examination of the blood and the identification of the various forms of abnormal cells is an important means employed in diagnosis of the different anemias (p. 68). Only the more outstanding abnormalities can be touched upon here. The least pronounced departure from the normal blood picture is an increase in the number of reticulocytes (see frontispiece). These young red cells resemble the ordinary cells in every way except that after

supravital staining (alcoholic solution of brilliant cresyl blue added to blood in the fresh state) fine reticulum of basophilic material can be seen in the cytoplasm. The reticular material is of cytoplasmic origin and does not represent a nuclear remains. A reticulum of similar nature may sometimes be seen in cells in which the nucleus is still intact. In normal human blood the reticulocytes are from 0 to 2 (av. 0.8) per cent of the total red cell count. They are increased after hemorrhage, at high altitudes (p. 9), exercise, in acholuric jaundice (p. 61) and pernicious anemia, especially following specific treatment (p. 64) of the latter condition and during the blood crises. A rise in the reticulocyte count indicates an increased activity of the blood forming tissue—the bone marrow—when

as a result of a specific stimulus turns out a large number of young cells. The maturation of red cells, that is, the change from reticulocytes to erythrocytes, has been estimated to take from 10 to 24 hours.

The next stage in the life of the red cell is represented by the *normoblast*, which appears in the blood in several different types of anemia. This cell, as its name implies, is normal in size and shape, possesses the usual amount of hemoglobin, but contains a nucleus. The bone marrow normally holds large numbers of these immature cells, but in health they do not reach the general circulation. In pernicious anemia and other severe types of anemia large, pale, nucleated cells are seen resembling white cells (lymphocytes, p. 70). They constitute, however, a very primitive stage in the development of the red cells; they are termed *megaloblasts*. The megaloblast contains a small amount of hemoglobin, sometimes almost none. Its protoplasm contains a diffuse or punctate arrangement of basophilic material. Hemoglobin is acidophilic, so these cells stain with acid as well as with basic dyes. This phenomenon of dual staining which may also be shown by some of the

abnormal cells, is known as *polychromasia*. Other cells of various sizes and shapes may be seen in the anemias. Shrinkage of the contents of the red cell with wrinkling of its limiting membrane, as may result from immersing the cells in a hypertonic solution, is termed *crenation*. In pernicious anemia, in particular, the presence of cells of unequal sizes (*anisocytosis*) and of deformed outline (*poikilocytosis*) is common. The poikilocytes may assume the most bizarre forms; mulberry, crescent, flask or hammer shapes may appear. *Macrocytes* and *microcytes* are terms denoting cells of usual structure and without

nuclei, but larger and smaller respectively than the normal erythrocyte. In certain conditions, e.g., lead poisoning, fine dots of basophilic material, probably a porphyrin (p. 40) appear throughout the cell, giving it a stippled appearance. This abnormality is known as *punctate basophilia* (see frontispiece). In certain types of anemia rings or twisted strands of basophilic material may be seen near the periphery of the cell. These are derived from the nucleus and are known as *Cabot's rings*. At other times small nuclear fragments—*Howell-Jolly bodies*—are present in the cytoplasm.

CHAPTER III

THE BLOOD VOLUME. WATER BALANCE

It has already been pointed out that a red cell count is merely an index of the relative proportions of cells to plasma and does not permit one to say whether the body's total supply of erythrocytes is increased or diminished. The same is true, obviously, for a hematocrit determination. These two methods indicate the concentration of the blood in erythrocytes. As a general rule, however, since the volume of the blood tends, through changes in its fluid content, to regain its normal level after this has been reduced or increased, the concentration of red cells does parallel the body's total supply. Yet it will be clear from the following examples that the principle upon which these methods are based does not imply any such relationship. If an erythrocyte count be made immediately after a sudden hemorrhage, it will be found to be practically normal, since by this time little or no fluid has passed from the tissues into the blood vessels to replace the lost blood, that is, to dilute what remains in the vessels. On the other hand, if a quantity of fluid be injected into the veins of an animal the blood count will be reduced, yet no reduction in the total number of cells has occurred. Had there been no previous knowledge of the conditions present in either of these instances, the red cell count would have given quite erroneous information regarding the body's total supply of erythrocytes. This may all seem very obvious to the reader, yet before clinical methods had been devised for the measurement of the blood volume, many wrong conclusions had been drawn concerning certain types of anemia. Blood volume estimations are of value in many clinical conditions associated with a loss or gain of fluid by the body, or for the purpose of checking the results of corpuscular and hemoglobin estimations. It is also sometimes of interest to know, in experimental investigations and in metabolic studies in man, the total amounts of certain blood constituents e.g., protein, calcium, sodium, etc., as well as their concentrations.

METHODS FOR THE ESTIMATION OF BLOOD VOLUME

DIRECT METHOD

The first attempts to measure the total quantity of blood in the body were made upon animals by Weicker (1954). His method consisted in taking a small

measured quantity of the animal's blood and diluting it to 1 in 100 with normal saline.

The animal was then bled, and after the blood had ceased to flow, its vessels were washed out and the muscles minced and extracted with water. Water was then added to the collected fluid—blood and washings—until its color matched precisely the tint of the original diluted blood specimen. The total collected fluid divided by 100 gave the blood volume.

This method was also employed upon decapitated criminals (Bischoff) in order to obtain a value for blood volume of man. By this method the total blood of the body was found to be about $\frac{1}{4}$ of the body weight—that is, from 5 to 6 liters (9–11 pints) in a man of average weight.

Obviously Weicker's method is applicable only to physiological problems of the laboratory. Furthermore, it is not free from serious errors. (1) The coloring matter of the muscles interferes with the colorations. (2) The turbidity of the final solutions prevents exact color matching, and (3) the loss of blood pigment as a result of intravascular as well as extravascular clotting is considerable and leads to further error.

INDIRECT METHODS

Carbon monoxide method

For the determination of the blood volume during life one or other of two methods may be employed. The first of these is the carbon monoxide method originally devised by Grehant and Quinquaud for animals, and modified by Haldane and Smith for man. The principle of this method is based upon the following facts (a) carbon monoxide when it combines with the blood pigment (hemoglobin) gives a bright cherry red color to the blood, so that the amount of the compound formed may be estimated colorimetrically, (b) carbon monoxide displaces oxygen from hemoglobin volume for volume.

The method is carried out as follows—the oxygen capacity of the subject's blood, that is, the maximum amount of oxygen which 100 cc. of his blood will absorb—is first determined. The oxygen capacity of normal blood is around 20 cc. Since the volumes of CO and O₂ that a given quantity of hemoglobin will take up are equal this determination gives the CO capacity as well. The subject is then instructed to breathe a known amount of CO (say 110 cc.) from a bag. Subsequent color comparisons of the blood with standard color solution show that the absorption of this quantity of gas has saturated the blood say to 12 per cent of its capacity. It is a simple matter of calculation to determine from this datum how much

as would be required to saturate the blood to its full capacity, and so arrive at the total blood volume. Thus—

After the inhalation of 110 cc. of gas the blood is found to be 12 per cent saturated; therefore $10 \times \frac{100}{12} = 916$ cc. of gas would be required to saturate it to full capacity. Inasmuch as each 20 cc. of gas would represent 100 cc. of blood if this were fully saturated $\frac{916}{20} \times 100 = 4580$ cc. total blood volume.

The carbon monoxide in the blood may be estimated more accurately by gas analysis after the method of Van Slyke rather than colorimetrically. The technical difficulties of the carbon monoxide method of determining blood volume are great, and the error would appear to be considerable.

THE DYE METHOD

This method was originally devised by Keith, Rowntree and Geraghty and has largely superseded the carbon monoxide method. The degree of dilution in the plasma of a known amount of dye injected into the circulation is employed as the basis of calculation. The color of the stained plasma is compared in a colorimeter with that of a standard dye solution of known concentration. There are several qualifications required of a dye before it can be considered suitable for blood volume measurements. In the first place, of course, it must be innocuous. It must not diffuse too rapidly from the blood stream; it must color only the plasma, and not be adsorbed by the cells of the blood nor by the walls of the blood vessels. Finally, it must not change color itself after entering the blood, nor cause the liberation of pigment from the red cells (hemolysis). If it lacked these qualifications, the colorimetric readings obviously would be in dependable.

The dye most commonly employed until recent years was brilliant vital red. The method has been improved by Gregersen and his associates by the use of the blue dye T-1824 (Evans blue). Evans blue has the advantage that the error due to any discoloration of the plasma by hemoglobin (hemolysis) is minimized. This dye is also eliminated very slowly (4.8 per cent per hour) from the circulation. The color determinations are made most satisfactorily with a photoelectric colorimeter or a spectrophotometer. In the method as modified by Crooke and Morris, the proteins of the plasma samples are precipitated and removed by filtration and the colorimetric

measurements made upon the filtrate. The following is the technic employed by these authors.

Six ml. of blood are drawn from a median antecubital vein for making up a standard solution. Five ml. of a 0.70 sterilized Evans blue solution are injected through the same needle. At intervals of 20, 40 and 60 min., 3 ml. samples are drawn from the opposite antecubital vein. All samples are transferred to 15 ml. centrifuge tubes, which have been coated with paraffin wax, and which contain 30 mg. of a 2:3 mixture of potassium and ammonium oxalates. After mixing, the tubes are centrifuged for 10 minutes at 2500 revolutions per minute. The plasma is immediately removed and kept in stoppered tubes for analysis. The proteins of the plasma samples are precipitated by adding slowly 7 ml. of the precipitating reagent (1 vol. concentrated HCl and 6 vol. alcoholic phosphotungstic acid) to 1 ml. of plasma. The samples are centrifuged and the supernatant fluid removed for colorimetric determinations. A standard solution is made up by adding 0.10 ml. of a 1 in 50 dilution of the injection solution to 1 ml. of undyed plasma. Of this mixture, 1 ml. serves as a standard. This quantity of the standard solution contains 1/2500 of the total amount of dye injected; such a dilution corresponds, therefore, to a "plasma volume" of 2500 ml. A color measurement is then made on each sample.

The calculations are made as follows. When P is the plasma volume, V_1 the mean value of the colorimetric readings of the three plasma samples and V_2 the value for the standard, then

$$P = \frac{V_2 \times 2500}{V_1}$$

In order to obtain the value for the total blood volume the proportion of red cells to plasma must be determined by means of the hematocrit. If the packed cell volume is 45 per cent the plasma volume is, therefore, 55 per cent and the total plasma volume, as determined above, is, say $\frac{3000}{55} \times 100 = 5454$ cc. total blood volume.

The determinations are made with the patient recumbent and under basal conditions, some 12 to 14 hours after a meal. The loss of dye into the tissues at the site of injection must be avoided since this of course will vitiate the results which, since the plasma would be less deeply stained, would be too high. Care must also be exercised to prevent evaporation of fluid from the samples after they have been drawn. Otherwise the concentration of dye in the plasma would be raised and the readings (which would indicate a lower degree of dilution) would be too low. Determinations by the dye method from time to time on the same individual under comparable conditions give consistent results. The absolute blood volume of course will never be known exactly, since it cannot be measured

directly in the living subject. But even in the dead subject there is no reason to believe that the direct method is any more accurate than the dye method in the living.¹

NORMAL VALUES FOR PLASMA AND WHOLE BLOOD VOLUMES

The whole blood is about 1/11 and the plasma 1/20 of the total body weight, i.e., 9 and 5 per cent respectively. Expressed as volumes, the whole blood is about 90 cc. per kilogram of body weight and the plasma about 50 cc. per kilogram. The blood volume of an average sized man of normal weight (70 kgm.) is therefore around 6000 cc. Rowntree has demonstrated that the blood volume is a function of the body's surface area. It amounts to about 3.3 liters per square meter (p. 533). The blood volume per square meter is higher by about 7.5 per cent in men than in women; the plasma volumes in the two sexes are, however, about the same. That is, the larger volume in males is due to a greater number of red cells. Infants have a greater blood volume in proportion to their body weight than have adults, but a lower volume in relation to body surface. (The body surface of children is of course greater in proportion to weight than that of the adult). The greater blood volume of the infant in relation to weight is due mainly to the greater numbers of red cells, though there is also a greater plasma volume.

REGULATION OF THE BLOOD VOLUME AND THE BODY'S WATER BALANCE

The blood volume and its variations cannot be considered apart from the fluid content of the body as a whole. The blood plasma constitutes but a small proportion of the total water of the body, being about 5 per cent of the body weight, whereas the extravascular fluids (extracellular 15 per cent, intracellular 50 per cent) make up 65 per cent of the weight of the body. Blood volume regulation is a question of balance between the fluid within the vessels and in the tissues. When conditions arise which tend to lower or raise the volume of blood, counter forces (p. 26) come into play which restore the normal level. When circulating fluid is lost, the vessels replenish themselves from the extravascular spaces. On the other hand, any tendency for the blood volume

to rise is met by a discharge of the excess into the tissues or along the excretory route. So, a balance is struck, and in health the blood volume is maintained remarkably constant. For example, after the intravenous injection of a large quantity of saline, the volume of circulating fluid (though raised temporarily) is brought back to normal within 30 minutes or less. On the other hand the loss of blood fluid, as by hemorrhage, immediately calls into action processes which may, in a remarkably short space of time, replenish the blood volume. When an animal is bled to death, at a not too rapid rate, the blood which is withdrawn is found after a few minutes of bleeding to have become diluted—demonstrating the promptness with which water (water and salts) has been absorbed into the vessels.

A. THE WATER INTAKE

The fluid of the body is replenished in two ways: (a) by the ingestion of liquids of moist food; (b) by the water formed in metabolism through the oxidation of the hydrogen of the food, and from the body tissues themselves. The following table from Rowntree compiled from the data of Magnus-Levy gives the quantities of water produced by the metabolism, respectively, of the three main food stuffs and of alcohol.

100 grams of fat	yield	107.1 grams water
100 grams of starch	yield	55.1 grams water
100 grams of protein	yield	41.3 grams water
100 grams of alcohol	yield	117.4 grams water

An ordinary mixed diet yields in this way 300 to 350 grams of water daily, or about 10 grams per 100 Calories. When no food or water is taken, the body materials themselves are used for this purpose, the glycogen protein and fat supplying important quantities of water. The camel's hump, for instance, which is largely composed of fat, is a reservoir for large amounts of water, and the clothes moth kept in a desiccated and fed upon perfectly dry food lays eggs which are 80 per cent water.

B. THE WATER OUTPUT

Water is lost from the body in the feces, in the urine and saliva and by the evaporation of water from the skin and lungs. The daily loss through these several channels is given in the following

¹ The blood volume as estimated by the foregoing procedures gives the volume of circulating blood and does not include the blood of the spleen (p. 53) which plays the rôle of a reservoir.

an averaged sized man at light occupation in a temperate climate.

Water (at average temperature and humidity).....	500
Inspired air (at average temperature and humidity).....	350
Expired air (at average temperature and humidity).....	1500
Sweat.....	150
Total.....	2500

The loss in the saliva is negligible under ordinary circumstances but may be considerable in mouth breathing (as a result of evaporation) and in those addicted to the spitting habit.

The water lost by the skin and lungs varies greatly with the temperature and relative humidity of the atmosphere and with the extent of the muscular exercise indulged in. At ordinary temperatures the loss of water by the skin is not perceived, since the sweat evaporates as quickly as it is formed. This insensible perspiration, as it is called, also includes the evaporation of water from the surface of the body apart from actual sweat secretion (see p. 626). The amount of the *insensible perspiration* has the average value given above but may be many times this value. When the air is hot, for example, the rate of sweat secretion and the rate of evaporation are greater than at lower temperatures. Relative humidity and air movement also influence the rate of evaporation. So, in humid, still atmospheres sweat secretion is more evident though it may be no greater than in a drier atmosphere when evaporation is more rapid. Large quantities of sweat are secreted as a result of muscular exercise or when as in the tropics the temperature is high. In hot climates the daily secretion may amount to 3000 cc. daily and in very torrid atmospheres it may be as much as 10 liters. This necessitates the drinking of an equal quantity of fluid in order to maintain the normal water content of the body, since the intake must equal the output. For the adult, the water requirement from all sources and under ordinary circumstances is around 2500 cc. daily or about 100 cc. per Calorie of food intake. This usually means that about 800 cc. exclusive of that derived from solid and semi-solid food must be drunk.

At ordinary temperatures the inspired air contains negligible quantities of water whereas the expired air is almost saturated with moisture. Any condition which increases the pulmonary

ventilation therefore increases the water lost by this route.

Protein is laid down in the body with water (about 3 grams of water per gram of solid). During growth or convalescence from wasting diseases retention of water therefore occurs, i.e., the intake of water including that derived from solid food exceeds the output. Fat and glycogen however are accompanied by a relatively small water storage. Water retention occurs following a change from a high fat to a high carbohydrate diet; on the other hand, water is lost from the body when the diet is changed from carbohydrate to fat. These facts are difficult to explain but they are not due, as was previously supposed (Zuntz), to a large volume of water being bound to glycogen. A high or low intake of sodium chloride causes an increase or decrease, respectively, in body water (see p. 407).

DEHYDRATION

When the output of water exceeds the intake, the body's water content obviously will be reduced. That is, the body is in negative water balance and the condition known as dehydration results. The following are the average normal percentages of water in several tissues:

	per cent
Muscle.....	75-80
Connective tissues.....	60
Adipose tissue.....	20
Bone (marrow-free).....	25
Blood:	
Plasma.....	92
Cells.....	60
Nervous tissue:	
Gray matter.....	85
White matter.....	70

Water composes about 70 per cent of the body's weight, the extracellular fluids accounting for about 20 per cent. The muscles contain about half, the skin a fifth and the blood only about a fourteenth of the body's water. Body water is practically all in the free state. That is, substances can be dissolved in it and it can be entirely removed by ultrafiltration. In other words, the quantity of so-called "bound" water, i.e., water bound with colloids or in other ways, is negligible. Water may be lost from the tissue cells or from the tissue spaces and blood, or from both intracellular and extracellular sites. Gamble, Ross and Tisdall therefore partition body fluid according to its location into two portions. In the

interstitial fluids and blood, the concentration of potassium is only a very small fraction of the sodium concentration. In the tissue cells, on the contrary, the concentration of Na is much less than that of K (see table 3½). The Na and K contents of the water excreted in certain pathological states is therefore employed as a means of estimating the proportions derived from extracellular and intracellular sources respectively. Thus, during the subsidence of nephritic edema, or of the subcutaneous accumulations in myxedema following thyroid treatment, the excreted water contains a large excess of sodium over potassium. During the fluid loss which results from a diet of glucose and water the loss of extracellular fluid as well as the shrinkage of the tissues causes an increased excretion of both Na and K (Byrom).

TABLE 3½
Concentrations of base in the water of blood plasma and in the water of muscle tissue
(After Gamble, Ross and Tisdall)

	PER 100 CC. PLASMA	PER 100 CC. PLASMA WATER	PER 100 CC. MUSCLE TISSUE	PER 100 CC. MUSCLE WATER
	mg.	cc. 0.1 N	mg.	cc. 0.1 N
Na ⁺	330	157.7	80	45.8
K ⁺	20	5.6	320	108.0
Ca ⁺⁺	10	5.5	8	5.3
Mg ⁺⁺	3	2.7	21	23.0
Total.....		171.5		182.1

Water of blood plasma is taken as 91 per cent by volume and water of muscle tissue as 76 per cent of weight.

In the early stages of a fast the excreted water has a high sodium content; after prolonged fasting its relatively high potassium content indicates an intracellular origin (pp. 608, 631). A loss of one-fourth of the body water is usually fatal.

Causes of Dehydration

Dehydration may result from:

(a) Simply the *deprivation of fluids*, for under such circumstances water, though its excretion in the urine and sweat is reduced, continues nevertheless to be lost from the body in considerable amounts. At high environmental temperatures or in fever, the condition will supervene more rapidly owing to the greater loss from the lungs and skin. Mental patients may readily become dehydrated as a result of their refusal to drink.

(b) *Excessive loss of water* may result from persistent vomiting (e.g., pyloric or intestinal obstruction) prolonged diarrhea, or the excretion of large quantities of urine or sweat, especially when accompanied by a restricted water intake. In the acute diarrheas of infants, dehydration and loss of weight may occur very rapidly.

(c) *Reduction in the total quantity of electrolyte* in the body fluids. The electrolytic concentration of the body fluids, both extracellular and intracellular, is maintained constant through the elimination or retention of water. That is, a reduction or increase in the total electrolytes which comprise chiefly the basic radicles Na (extracellular) and K (intracellular) and the acid radicles HCO₃ and Cl, is accompanied by a corresponding decrease or increase in the volume of body water. The sum of the basic elements and acid elements of course must balance. Loss of Cl can be made good by the retention of H₂CO₃ and a rise in plasma bicarbonate. Excreted base, however, can be replaced only by basic substances supplied in the food. The total concentration of electrolytes in the body fluids is therefore dependent upon the stores of total base. For example, in pyloric or high intestinal obstruction (p. 510) fluid is secreted in large quantities into the gastrointestinal tract. The fluid may be vomited or may collect and remain in the dilated part of the canal above the obstruction. (The latter occurrence is the rule in the rabbit which cannot vomit.) In either case the secretion of large quantities of gastric juice entails loss of blood chloride. A similar chloride loss is induced in animals by means of a gastric fistula fashioned by sectioning through the pylorus, stitching the stomach opening to the abdominal wall and allowing the gastric juice to drain to the exterior. In the foregoing instances, the chloride depletion causes at first no ill effects, the normal concentrations in electrolytes of the blood and tissue fluids being maintained for a time by the retention of CO₂, and, as a consequence of this, an increase in bicarbonate. The compensation for the Cl loss leads however to alkalosis which is then countered by an increased excretion of base in the urine. This of course is accompanied by diuresis; marked dehydration results.

On the other hand, the continued loss of pancreatic juice (p. 451) to the exterior causes immediate depletion of base; plasma bicarbonate is reduced. In the adjustment of the acid-base balance the excess of acid radicles is excreted in urine; this again entails a loss of water. Similar

the ingestion of acid-producing salts causes a depletion of base, which is used for the neutralization and excretion of the acid radicles. Such salts therefore act as diuretics and dehydrating agents.

(d) *The injection of hypertonic solutions* (p. 30) into the blood stream. When a strong sugar or salt solution is injected, the temporary rise in the osmotic pressure of the blood causes a flow of fluid from the tissues into the vascular system until equilibrium is re-established. The blood volume is increased, but is soon returned to normal by the loss of the excess fluid into the tissues and its eventual excretion via the kidney and bowels. A net loss of body water results.

Effects of dehydration

(a) *Loss of weight* due to the reduction in tissue water as well as to the actual breakdown of body substance which occurs in the effort to furnish water for the maintenance of physiological processes. Fat and carbohydrate stores are first drawn upon for this purpose and later protein. (b) *Disturbances in acid-base balance* usually toward the acid side. The diminished quantity of circulating fluid (anhydremia) and the consequent depression of oxidative processes in the tissues is held responsible for the excessive production of acid metabolites, e.g., lactic. The slowing of the renal circulation also leads to a reduced excretion of urine and the retention of acids (e.g., phosphoric) which under normal circumstances are eliminated. (c) *Rise in the non-protein nitrogen of the blood*. (d) *Rise in body temperature* as a result of the reduction in circulating fluid (see p. 624). (e) *Thirst*. Under normal circumstances this serves as a signal that the water stores of the body require to be replenished. Any fall in the water content of the tissues is reflected in the glandular activities especially of the salivary glands. Secretion is suppressed; the mouth and throat become dry and the sensation of thirst is aroused. In dehydration thirst is extreme and the mouth parched. (f) *Dryness, wrinkling and looseness of skin* and a pinched expression to the features result from the loss of subcutaneous fat and of water from the deeper layers of the skin. Other manifestations are, reduced intraocular tension and recession of the eyeball and, in infants, depression of the fontanelle.

WATER INTOXICATION

When an animal is given large quantities of water by stomach tube, especially if urinary secre-

tion is reduced by the administration of pituitrin, the tissues become "water-logged," serious symptoms ensue, e.g., depression of temperature, vomiting, convulsions and coma, which shortly end in death. Similar effects also follow in man if large quantities of water are given to a patient with nephritic edema or if in a subject of diabetes insipidus pituitrin be administered while the water intake is maintained at the usual level (see p. 739). The convulsions are probably the result of cerebral edema.

ALTERATIONS IN BLOOD VOLUME

I. REDUCTION OF THE BLOOD VOLUME

This may result from:

- (1) A loss of *whole blood* as in hemorrhage (p. 20).
- (2) *Reduction in the total number of red cells*, as a result of increased destruction or diminished production (see anemia p. 61).
- (3) Loss of *plasma* alone from the vessels as in extensive burns p. 261 or
- (4) *Loss of blood water*. This is called *anhydremia* and is simply a part of a general dehydration and so results from the same causes as the latter.²

In the reduction of blood volume resulting from hemorrhage, the concentration of the blood in cells and protein is lowered, since a watery fluid is attracted into the vessels from the surrounding tissues.

When the blood volume is lowered as a result of a loss of plasma, the red cell concentration is increased but the protein (hemoconcentration) of the plasma is little altered.

In anhydremia both the protein concentration of the plasma and the red cell count are raised. The concentration of plasma protein may increase by 50 per cent or more. The viscosity of the blood is therefore raised; the blood appears "syrupey" and flows sluggishly from an opened vein. If the anhydremia persists the red cell count and the protein concentration tend to fall again as a result of red cell and protein destruction. Then an estimation of the blood concentration may fail to give a true index of the extent of the blood volume reduction.

Exposure to cold causes a moderate loss of water from the blood to the tissues (chiefly skin muscle and probably liver), the total water content of the body remaining unaltered. It is not alto-

² Variations in blood volume from time to time due to alterations in blood water may be detected from estimations of hemoglobin or protein concentrations, or by means of the hematocrit.

gether clear by what means this movement of water is brought about. It is, however, an important factor in the regulation of body temperature (p. 624). The work of Barbour and others furnishes evidence of a nervous element in the mechanism. Animals in which the cord had been divided in the upper thoracic region when placed in a cold bath did not respond in the normal fashion. Concentration of the blood did not result and the temperature of the body fell to that of the environment (fig. 244). The control is exercised evidently through vaso-motor nerves.

Barbour and Hamilton have shown that cold applied locally after section of the splanchnic nerves causes anhydremia as a result of the transudation of water into the skin of the cooled area. They attribute the migration of water to constriction of the cutaneous arterioles and consequent slowing of the capillary blood flow, which in turn, apparently through oxygen lack, increases the permeability of the capillary wall.² It is probable therefore that exposure to cold induces blood concentration through both central and direct peripheral effects.

Posture. The blood volume of the human subject after 30 minutes or so in the erect posture is some 15 per cent less than that in recumbency. A fluid of low protein concentration leaks from the vessels of the lower limbs into the extra-capillary tissues, as a result apparently of the increased hydrostatic pressure in the capillaries of these parts (p. 25, see also p. 382).

II. INCREASE IN BLOOD VOLUME

(1) *High temperatures.* Two factors are concerned in the elevation of the blood volume which follows a rise in environmental temperature, (a) contraction of the spleen whereby whole blood is discharged into the general circulation (p. 54) and (b) dilution of the blood, water being drawn from the tissues to augment the circulating fluid. This is a reversal of the mechanism described above as occurring at low temperatures. Sweating, and increased evaporation from the body surface, if over a prolonged period, will tend to counteract these effects; the blood volume may then show a decrease, or one effect may balance the other and no change occur.

(2) *Muscular exercise.* At the beginning of

² In this experiment, however, the cold was of such a degree that it may have directly damaged the capillary epithelium.

exercise the blood volume is increased as a result of the discharge of blood from the spleen. Inasmuch as the splenic blood is relatively rich in red cells, the blood of the general circulation shows an increased cellular concentration. Later, as osmotically active substances (e.g., lactic acid) are formed in the contracting muscles, water is attracted from the vessels. The protein concentration of the plasma, and the red cell count increase. Sweating, when it ensues, tends to increase the degree of anhydremia by causing a reduction in the water content of the body as a whole. The early increase in blood volume which in animals, results from the discharge of blood from the spleen is not seen, as a rule, in man. In dogs, muscular training causes an increase in blood volume and of the erythrocyte count which persists for about a month after the termination of the training period.

(3) *Emotional excitement* in animals and in man causes an increase in blood volume due to contraction of the spleen (p. 54).

(4) *Pregnancy.* Barcroft and his associates observed in sheep a pronounced increase in blood volume in the first and last thirds of pregnancy due to an increase in plasma. The corpuscular volume showed a relative decrease.

SUMMARY OF THE PATHOLOGICAL STATES ASSOCIATED WITH ALTERATIONS IN BLOOD VOLUME

Reduction

(a) *Hemorrhage* (loss of whole blood), (b) *burn* (loss of plasma), (c) *dehydration* (loss of water), (d) *pernicious anemia* (reduction in red cells with a moderate increase in plasma), (e) *chronic anemias other than those of the pernicious type*. In these the total volume of red cells is only slightly or moderately reduced and this is to a large extent compensated for by an increase in plasma above the normal standard. The total blood volume is therefore, as a rule, not greatly below normal as calculated upon the basis of weight or of surface area. In other words, the blood is diluted and if, as sometimes occurs, the increase in plasma is greater than the reduction in red cells, a red cell count will give an exaggerated picture of the oligocythemia. (f) *Obesity*. The blood volume per kilogram of body weight is much reduced but is normal when considered in relation to the body surface. (g) *Myxedema* (reduction of both red cells and plasma but mainly of the former (fig. 7).

Increase

(a) *Polycythemia vera* (increase mainly of red cells but also of plasma), (b) *cirrhosis* of the liver (increase of plasma), (c) *leukemia* (increase in white cells and plasma), (d) *splenomegaly* with anemia—Banti's disease (increase in plasma), (e) *hyperthyroidism* (equal increases both in red cells and plasma).

It should be pointed out that the proportions of red cells and plasma may vary from the normal though the total blood volume remains unaltered. With regard to the blood volume and the proportion of cells to plasma there are therefore nine possible blood states. Rowntree has introduced

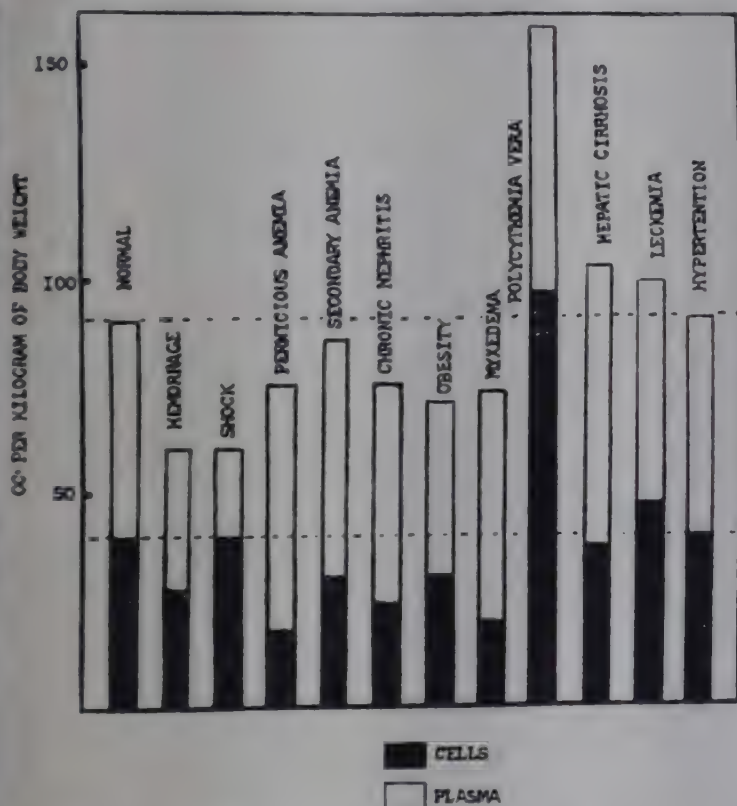


FIG. 7. Showing whole blood, red cell and plasma volumes in various diseases. Dotted lines indicate normal standards, upper for whole blood, lower for plasma (after Rowntree).

the following descriptive terminology. A normal blood volume he terms *normovolemia*. If the ratio of cells to plasma is normal as well, he calls the condition *simple normovolemia*; decrease or increase in the number of cells in relation to plasma is termed *oligocythemmic* or *polycythemmic normovolemia* respectively. *Hypovolemia* and *hypervolemia* are corresponding terms for reduced and increased blood volumes; each of these is divisible into simple, polycythemmic and oligocythemmic forms (see fig. 8).

THE EFFECTS OF HEMORRHAGE

When more than 30 per cent of the blood volume is lost rapidly the body is usually unable to repair

the loss unaided and, unless transfusion is resorted to, death results. In a healthy man the loss of 30 per cent or less of his blood, calls readjusting mechanisms into play which may bring the blood volume back to the normal level within a remarkably short time; 500 cc. or so of blood drawn for transfusion purposes are said to be replaced within an hour or so. The restoration of the blood to its previous concentration in erythrocytes, however, takes about seven weeks on the average. This time may be shortened considerably by the administration of iron and a diet containing a liberal quantity of high quality protein. Fowler and Barer found in a study of 200 blood donors that, after the removal of 550 cc. of blood, the average fall in hemoglobin was 2.3 grams per 100 cc. Regeneration of hemoglobin occurred at the rate of 0.049 gram per cent for men and 0.040 gram for women per day.

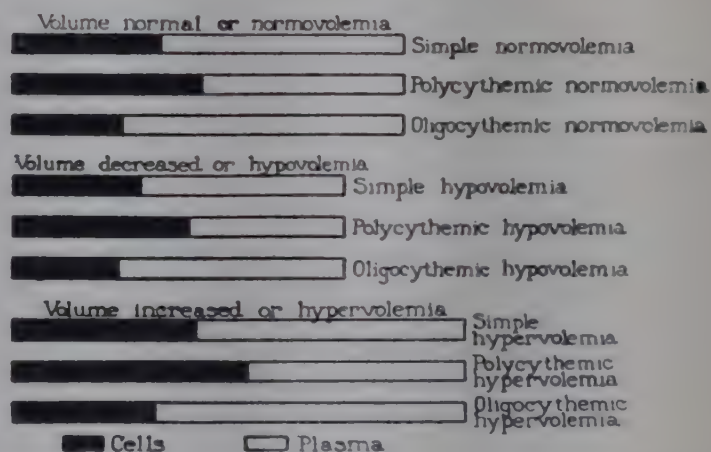


FIG. 8. The nine possible combinations of whole blood, plasma and red cell volumes (after Rowntree).

The protective mechanisms which automatically come into action after hemorrhage are several and may be divided into two groups—*immediate* or *early* and *delayed*.

A. Immediate or early effects

If the loss of blood is large, especially if it is of sudden occurrence and from an artery there is a prompt fall in blood pressure as a result simply of the reduction in circulating fluid (p. 122). If not too great, the fall in pressure is of benefit, since it helps to prevent further bleeding. A moderate loss of blood, 10 per cent of the total amount, produces little or no drop in pressure. This is especially true if the blood is lost gradually and if it comes from a vein, i.e., beyond the peripheral resistance. Under these circumstances compensatory mechanisms easily maintain the pressure of blood at its normal height.

Clotting of the blood (p. 88) which occurs within a few minutes serves to close the opening in the blood vessel. The initial drop in pressure, when such occurs, aids the formation of the clot and the effectual sealing of the vascular wound. This is also furthered in the case of an artery by the retraction of the middle fibro-muscular coat of the vessel, as well as by the curling up of its endothelial lining. These factors alone may be sufficient to stanch the flow of blood from an artery as large even as the popliteal. The blood also clots more rapidly than usual after a severe hemorrhage.

Increase in the heart rate. This is almost invariably an accompaniment of a severe hemorrhage and is one of the most valuable signs of concealed, i.e., internal, bleeding. It is brought about through carotid sinus and aortic reflexes (pp. 240 and 242) initiated by the fall in blood pressure. Reduction in blood flow through the vessels of the medulla with the consequent anoxemia of the cardiac centers may be an additional factor. Adrenaline liberation (p. 689) also probably plays a part. The increase in heart rate might under the circumstances appear to be of advantage—an attempt on the part of the heart to increase the rate of blood flow and so compensate for the reduced volume of blood by having it carry an oxygen load from lungs to tissues more frequently. It seems clear, however, from the work of several investigators (p. 216) that simple increase in the cardiac rate does not increase the output of the heart.

Contraction of the spleen and the discharge into the circulation of a large quantity of blood rich in red cells (p. 54).

Increased respiration. The anoxia of the chemoreceptors of the carotid and aortic bodies caused by the reduced blood flow (p. 346) is probably responsible for the increased rate and depth of breathing. When the blood loss is more profound, and consequently the oxygen want more urgent, long deeply drawn inspirations, and expirations of a sighing character ensue (air hunger), or periodic breathing of a Cheyne-Stokes type may develop (p. 352). Gasping respirations precede death.

Reduction in capacity of the vascular bed and redistribution of the blood. When the flow of blood has been stanching or considerably lessened by a complete or partial closure of the wound in the vessel, the blood pressure, if this had been lowered, rises again. This is the result mainly of a readjustment of the capacity of the vascular

system whereby it is made to conform more nearly to the lessened volume of blood. It is this reduction in the vascular capacity which prevents the initial fall in pressure when the loss of blood is gradual. It is effected by the reflex narrowing of innumerable small vessels (vasoconstriction) in regions such as the skin, mucous membranes, intestine and other parts not immediately essential to life. The vascular response is called into play by the underfilled state of the arteries and large veins feeding the heart (see vascular reflexes, pp. 240 and 241). This measure whereby the blood remaining in the vascular system is confined to a smaller space is of the utmost importance; it enables the essential centers in the medulla to be supplied with blood under adequate pressure to sustain their vitality. Also a greater quantity of blood than would otherwise be possible is brought to the heart to supply its muscle, fill its cavities and maintain the circulation. The withdrawal of blood from the less important parts of the body is responsible, however, for some of the characteristic manifestations of hemorrhage, notably the pallor of the skin and mucous membranes, and the coldness of the body surface. The cerebral anemia causes sensation of giddiness or faintness, flashes of light or ringing in the ears (tinnitus).

The rise in blood pressure at this stage is conducive to fresh bleeding. There is danger of the clot becoming dislodged.

B. Delayed effects

Replacement of the lost fluid. This, it has already been mentioned, commences almost upon the instant that the blood is lost (p. 16), but takes a variable length of time, depending upon the extent of the blood loss, to become complete. Fluid is drawn from the tissues into the vessels and dilutes the blood. The corpuscular concentration is therefore reduced. The protein concentration of the tissue fluid at first is relatively low so that a short time after hemorrhage the protein content of the plasma is markedly depressed. Very soon, however, the concentration of protein in the plasma shows a pronounced rise again as a result of the mobilization of protein stores. Calton found, for example, that in dogs 50 per cent of the plasma protein removed by bleeding was restored within 4 hours. The extreme thirst which the subject of acute hemorrhage suffers is the call of the tissues for fluid and indicates that their own stores are being drawn into the un-

filled vessels. The administration of water will therefore aid the body in recovering its water balance and replenishing the blood volume.

Replacement of the red and white cells finally occurs through the increased activity of the blood-forming organs. This takes several days or weeks, the rapidity of the process depending to a large extent upon the nutrition and recuperative power of the individual and upon the diet (pp. 21 and 57). While the repair process is in progress reticulated cells are found in increased numbers in the blood (p. 12).

THE FACTORS GOVERNING THE INTERCHANGE OF FLUID BETWEEN THE TISSUES AND THE VESSELS

The physical factors which determine the flow of fluid from the tissues into the blood stream as well as in the reverse direction—from the vessels to tissue spaces—are the *osmotic* and *hydrostatic pressures* of the fluids in the two situations.

Osmotic pressure

Osmotic pressure may be simply defined for our purpose here as the “attractive” or “drawing” force which sodium chloride, cane sugar and many other substances in solution exert upon the water molecules when water and a solution of one or other of these substances are separated by a membrane which allows the molecules of water to pass, but is quite or relatively impermeable to the molecules of the dissolved substance. Such a membrane is spoken of as “*semi-permeable*.” An example will make this clear.

If an aqueous solution of cane sugar be placed in a vessel and a layer of water poured gently upon its surface, the two liquids will remain separate for a time. Gradually, however, sugar molecules will diffuse upwards and intermingle with the water molecules, while many of the latter will pass downwards into the sugar solution. The diffusion process, which is quite independent of gravity or convection currents, will continue slowly until the concentrations of the two types of molecules become equal throughout all parts of the liquid. If now instead of allowing free diffusion between the two solutions to take place, they be separated by a membrane which will permit the molecules of water to pass through it, but will offer a barrier to the migration of the dissolved substance, equal and free diffusion cannot occur. Since the water is able to pass into one compartment while the sugar molecules cannot pass out, the volume in this latter compartment obviously must increase; the pressure will rise. The pressure which is developed may

amount to several atmospheres. This is the osmotic pressure, and it may be measured by the apparatus shown in fig. 9, A. As the osmotic pressure within the inner chamber increases the mercury column is raised, that is, work is performed. In order to drive water through the membrane into the outer chamber the osmotic force must be overcome. In fig. 9, B is illustrated a cylinder fitted with a piston and closed at its lower end by a semipermeable membrane. A force greater than the osmotic pressure developed within the cylinder would be required in order to filter water through the membrane. An instrument which measures osmotic pressure is known as an *osmometer*. An indirect method maybe employed, e.g., measurement of the freezing point or the vapor pressure.

It is seen therefore from the foregoing that what was spoken of as an “attractive force” is simply the usual diffusion of water molecules into a solution of sugar which, owing to the intervention of a semi-

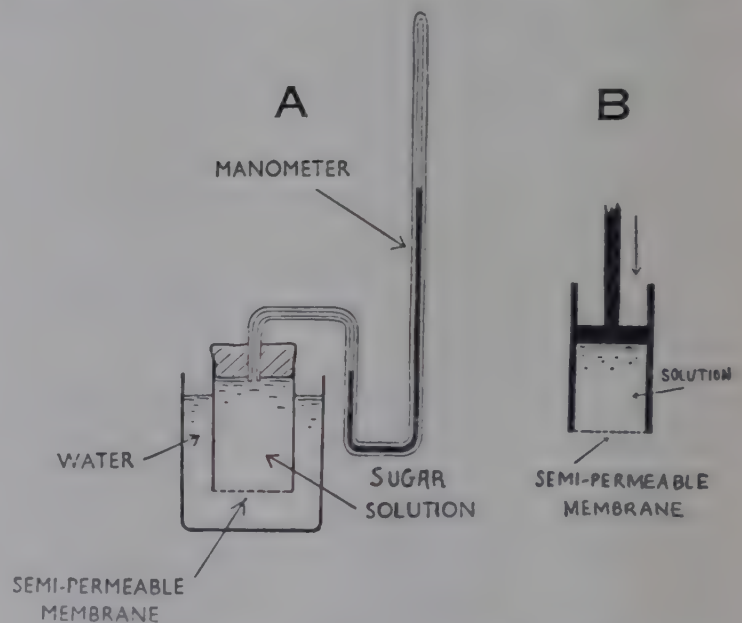


FIG. 9. Description in text (after Parsons).

permeable membrane, cannot diffuse in the opposite direction. The actual pressure developed may be supposed to result from the bombardment of the walls of the containing vessel by the imprisoned molecules of the dissolved substance.⁴ The osmotic pressure of any solution will then necessarily depend upon the number of the bombarding molecules, i.e., upon their concentrations in the solutions. The pressure of a gas also depends upon the number of gas molecules per unit volume, and indeed it has been proved that the gas laws can be applied to the behavior of dilute solutions of cane sugar and other substances which exert osmotic pressure.

In other words, *substances in dilute solutions behave almost precisely as though they were in a gaseous state*. For instance, an amount of any gaseous substance equal to its molecular weight in grams (gram molecule)

⁴ Several theories, of which this is the simplest, have been advanced to account for the phenomenon of osmotic pressure.

at standard temperature and pressure has a volume of 22.4 liters. That is, 32 grams of oxygen at 0°C. and 760 mm. Hg occupy the same volume (22.4 liters) as 2 grams of hydrogen under the same conditions. Also, according to Avogadro's hypothesis, equal volumes of gases at the same temperature and pressure contain equal numbers of molecules, i.e., their molecular concentrations are identical. The molecular weight of cane sugar is 342 grams. Therefore, according to Avogadro's law 342 grams of cane sugar if in the gaseous state would have a volume, at standard temperature and pressure, of 22.4 liters. Conversely, 342 grams of cane sugar if confined to a volume of 22.4 liters by dissolving it in that amount of water will, if the gas laws apply, have a pressure of 760 mm. Hg at 0°C. Again, according to Boyle's law the pressure of a gas is inversely proportional to the volume at constant temperature. If therefore the same amount of cane sugar be dissolved in half the amount of water (11.2 liters) the osmotic pressure will be doubled. On the other hand, if the concentration of the molecules of sugar be reduced by dissolving them in double the quantity of water (44.8 liters) the osmotic pressure of the solution will be halved. Also, as in the case of a gas, the osmotic pressure of a substance in solution is proportional to the absolute temperature.

The applications of the gas laws to the development of osmotic pressure by substances in solution may be stated as follows.

(1) *Avogadro's Law.* Any two gases of equal volume at a given temperature and pressure contain the same number of molecules. A molecular weight of a gas at 0°C. and 760 mm. Hg pressure occupies a volume of 22.4 liters. So, an amount of substance equal to its molecular weight in grams if dissolved in 22.4 liters of water at a given temperature has an osmotic pressure equal to the pressure which it would exert were it in the gaseous state, namely 760 mm. Hg.

(2) *Boyle's Law.* The osmotic pressure is proportional to the molecular concentration if the temperature remains constant. (See also p. 314.)

(3) *Law of Gay-Lussac.* The osmotic pressure is proportional to the absolute temperature if the molecular concentration be constant.

(4) *Dalton's Law of Partial Pressures.* If several substances are present in a solution, the osmotic pressure exerted by each will be the same as if it were present alone in the solution. In other words, the total osmotic pressure exerted by a solution containing a number of different substances is the sum of the osmotic pressures exerted by each individually.

These laws apply with remarkable precision to dilute solutions, but in the case of concentrated ones, though there is a general agreement with the behavior of gases, other factors enter in which make the applications less perfect. Also substances generally classed as electrolytes (p. 99), sodium chloride for instance, exert osmotic pressures which are much higher than those of non-electrolytes, such as cane sugar or glucose.

This apparent departure from the general principle is due to the fact that each molecule of the electrolyte is split into two parts (ions) and each of these acts as a separate particle and exerts its pressure effect. A sodium chloride solution, therefore, as a result of the dissociation has twice as many active particles as a cane sugar solution even though the number of molecules in a given volume (molecular concentration) of each be the same.

The semipermeability of the membrane, must be emphasized, is an essential factor in the development of osmotic pressure. A solution may possess a very high osmotic pressure when separated from water by a membrane which does not allow the dissolved molecules to pass, but will exhibit no osmotic pressure when separated from water by a membrane perfectly permeable to the substance in solution. Certain membranes, for example the envelope of the red cell, are impermeable to potassium, sodium and calcium, but permeable to water. Others—such as the capillary wall—offer little hindrance to the passage of crystalloids. In the former case, osmotic pressure changes can be brought about within the cell by altering the concentration of sodium chloride in the plasma (p. 48). But in the latter case sodium chloride and other crystalloids, e.g., glucose, urea, bicarbonate, etc., though in the concentrations in which they exist in plasma are capable when placed in an osmometer of developing a pressure of several atmospheres, exert a negligible effect on osmotic pressure within the capillary since the membrane of the latter is fully permeable to them.⁶ The colloid osmotic pressure of the plasma is less than 1 per cent of the total osmotic pressure, i.e., of the osmotic pressure as measured in an osmometer.

Osmotic pressure is one of the fundamental factors underlying many physiological processes in both animal and plant life, e.g., the excretion of urine, the interchange of materials between the interiors of blood cells or tissue cells and their surroundings, the flow of sap in plants, as well as the regulation of blood volume. The fluids of the body contain various electrolytes and organic materials in solution. So permeable membranes of various types possess different selective permeabilities, such as the cell wall, the vascular endothelium, the renal epithelium, the membranes lining the serous cavities and the alimentary tract, are interposed between fluids cap-

⁶ It should be mentioned however that sudden changes in concentration of these substances (as in intravenous injection) will result in temporary disturbances of osmotic relationships while they are diffusing to re-establish equilibrium.

of developing different osmotic pressures. The osmotic pressures are however not constant, but vary from time to time as a result of metabolic processes and the changes in concentration of various constituents of the intracellular and extracellular fluids incident thereto. Furthermore, the permeability of living membranes is not fixed and unalterable but is modified by several factors. Sodium and potassium chlorides, for example, increase membrane permeability to water, the chlorides of calcium and magnesium decrease it; permeability also probably is increased by a rise in temperature and the eggs of various marine forms (*Echinoderm*, *Arbacia* etc.) become more permeable after fertilization. Narcotics, on the other hand, in non-toxic doses decrease the permeability of the cell to water.

ISOTONIC, HYPERTONIC AND HYPOTONIC SOLUTIONS. When two solutions are placed one on either side of a semipermeable membrane and the molecular concentrations of the dissolved substance is such that no osmotic pressure is developed, the solutions are said to be *isotonic*. That is, the pressures on the two sides of the membrane precisely balance one another. When one solution has a higher osmotic pressure than the other it is said to be *hypertonic*; the solution of lower osmotic pressure is termed *hypotonic*.

Hydrostatic pressure

The other important factor in the interchange of fluid between the blood and the general body fluids is the hydrostatic pressure within the capillaries, i.e., the blood pressure, and its relation to that of the extravascular fluids.

The relation of osmotic to hydrostatic pressure in the interchange of fluid across the capillary membrane

It has already been mentioned that the substances in true solution in the plasma, such as glucose, inorganic salts, etc., exert little or no effective osmotic pressure within the capillaries. Their molecules are of such a size that they pass relatively freely through the "pores" of the membrane. Obviously this must be so, otherwise essential nutritive materials could not reach the tissue cells and waste products could not enter the blood stream to be excreted. It is otherwise with the plasma proteins which, owing to the very large size of their molecules, cannot pass readily through the normal capillary wall. The latter is not, however, quite as impermeable to the plasma colloids as has been thought—they "leak" into the extravascular spaces—so, the osmotic pressure which they exert in the vessel is somewhat less than the value obtained in the

laboratory. Since the albumin has the smallest molecule of the three plasma proteins, it escapes through the vessel in relatively greater amounts than the globulin and fibrinogen fractions.

The manner in which these two pressures—osmotic and hydrostatic—act in regulating the interchange of fluids between the tissues and the muscles may now be seen. The blood at the arterial end of a capillary has a pressure, let us say, of 30 mm. Hg. This is a force driving the water and the dissolved crystalloids through the capillary membrane. But the hydrostatic pressure of the tissue fluid on the outer side of the membrane offsets, in part, that within. The pressure of fluid in the tissue spaces is difficult to determine but it is considerably less than that in the capillaries. It probably varies considerably in different regions, being low in those containing much loose areolar tissue. For purposes of illustration let it be assumed to be 8 mm. Hg. The hydrostatic pressure, therefore, which is effective in forcing fluid out of the vessel (filtration pressure) is only the difference between the pressure within and that on the outside of the vessel, that is, 22 mm. Hg. The osmotic (protein or oncotic) pressures of the plasma and tissue fluids must be taken into account, however. In the plasma it amounts to about 25 mm. Hg. The tissue fluids have a lower protein content and consequently a lower osmotic pressure. The latter amounts to about 10 mm. Hg. The difference, i.e., 15 mm. in favor of the plasma will act as an attractive force to hold fluid within the vessels and so should be subtracted from the value of the effective hydrostatic pressure of 22 mm. as calculated above. The net result of these opposing forces will be the filtration of fluid through the vessels under a pressure of $(22 - 15) = 7$ mm. Hg.

Blood		Tissue fluid	
<i>Hydrostatic pressure</i> 30 mm. Hg	Capillary wall	<i>Hydrostatic pressure</i> 8 mm. Hg	
Effective hydrostatic pressure 22 mm. Hg			
<i>Osmotic pressure</i> 25 mm. Hg		Osmotic pressure 10 mm. Hg	
Effective osmotic pressure 15 mm.			
Driving force → 7 mm. Hg			

The osmotic pressure of the plasma, if anything, increases while the blood passes along the capillary as a result of the passage of water outwards and the consequent rise in the concentration of protein. That is, the force holding fluid within the vessel is increased. The hydrostatic pressure, on the other hand, falls gradually from the arterial to the venous end of the capillary. Near the arterial end, the blood pressure being greater than the osmotic pressure, a filtration of fluid

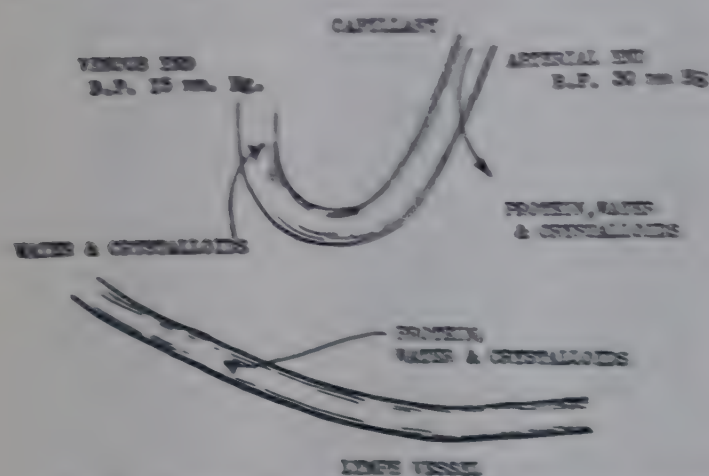


FIG. 10. Illustrating the relation of hydrostatic and osmotic pressures in the regulation of the interchange of fluid between the vessels and the tissue spaces.

with a low concentration of protein will result (see fig. 10). Near the venous end, the hydrostatic pressure falls below the osmotic pressure and a flow of dilute fluid (water and salts) from the tissue spaces into the blood takes place.⁶

⁶ It has been reported by McMaster and Rous that dye particles escape more readily from the venous end of the capillary. They conclude that the capillary permeability increases progressively from the arterial to the venous end. This implies that a steady fall in osmotic pressure would result as the venous end was approached since more protein would leak out.

Transudation of a dilute plasma and reabsorption of a saline fluid, respectively, are continually going on in these two regions of the capillary bed.

Metabolic processes in the tissues bring about changes whereby larger molecules are being broken down into smaller ones; other molecules are removed or built up into larger ones. In this way alterations in molecular concentration and in the diffusibility of the constituents of the tissue fluids with consequent variations in osmotic relationships are occurring ceaselessly.

Under any circumstance in which the blood volume is increased or diminished, either the hydrostatic pressure or the osmotic pressure, both are altered, and it is through such changes that the blood fluid is restored automatically to its previous level. After hemorrhage, for example, the hydrostatic pressure is lowered in the capillary area but the osmotic pressure is unchanged. Fluid will therefore be absorbed from the tissue spaces. Again, when water is drawn from the blood, in consequence of excessive loss of fluid by the kidney, sweat glands or bowels, concentration of the plasma proteins will result. The increased osmotic pressure of the plasma will hasten the rate of absorption from the tissues. The intravenous injection of large quantities of isotonic saline, on the other hand, will have twofold effect of diluting the colloids and temporarily increasing the hydrostatic pressure. The excess fluid in consequence is rapidly eliminated from the blood stream into the tissues and is excreted through the kidney and bowels.

If this conclusion is correct, it is difficult to see how filtration and absorption could occur in different parts of the same capillary and it would be necessary to consider the possibility that filtration occurs in some capillaries and absorption in others.

CHAPTER IV

THE LYMPH AND TISSUE FLUIDS

STRUCTURE OF THE LYMPHATIC SYSTEM

The lymphatic system commences peripherally as a meshwork of delicate vessels (lymph capillaries) which drain the tissue spaces. By the confluence of small vessels larger ones are formed which, receiving tributaries along their course, gradually swell in size, and finally form the right lymphatic and thoracic ducts. These pour their lymph into the blood stream by way of the right and left subclavian veins, respectively. The system is a closed one, its vessels possessing complete walls formed of endothelial cells.¹ But their walls as compared with those of the blood capillaries are extremely permeable; a dye such as T-1824 (Evans blue), which escapes very slowly from the blood stream, passes rapidly from the lymphatic vessels. Small nodes (lymph glands) are interposed in the course of the larger lymph channels. These vessels, upon reaching the gland break up into finer channels, which, plunging into the node, open into the sinuses of its cortex. After passing through the gland the lymph is collected again on the other side by fine vessels which soon re-form into a few larger trunks. The glands are placed at strategic points along the lymph routes, e.g., the elbow and axilla, knee and groin in the case of the upper and lower limbs, and at points in the abdomen, thorax and neck where several lymph vessels become confluent. Lymph vessels are situated in skin, in subcu-

taneous tissue, in the fascial planes of muscles, in the mucosa of the respiratory tract, in the submucosa and subserosa of the gastro-intestinal and genito-urinary tracts and in the capsule and septa of the liver. Those in the intestinal villi are known as *lacteals*. The lymphatic system of the heart consists of intercommunicating plexuses lying beneath the epicardium and the endocardium and within the myocardium. Lymphatics are also present in the areolar tissue underlying the peritoneum and pleurae. They are absent from the central nervous system. In inflammatory states the lymphatics show active proliferation.

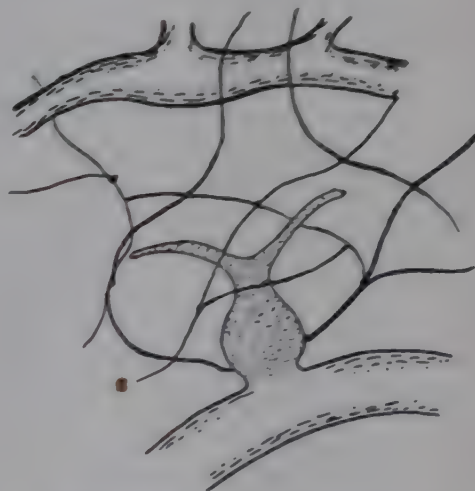


FIG. 11. Showing a lymph vessel arising from a vein (redrawn from Sabin).

The skin is supplied richly with lymph capillaries. The cutaneous lymph vessels are so abundant, according to McMaster, that the skin cannot be punctured anywhere without tearing them, and since the flow of lymph along these vessels is relatively rapid, foreign material injected into the skin soon reaches the regional lymph nodes. An injection into the skin is, therefore, an injection into the lymphatic system. The permeability of the lymph capillaries is increased by many agencies, e.g., sunlight, warmth, and mechanical stimulation. Their walls may become so permeable that they can scarcely be considered as channels walled off from the surrounding tissue spaces.

THE NODES AS DEFENSE BARRIERS

The lymph nodes must be looked upon as important structures for the defence of the blood

¹ The lymphatics develop from the endothelium of the veins, appearing in the embryo as offshoots or "buds" from the internal jugular, abdominal and iliac veins (fig. 11). The lymph vessels grow and extend by the proliferation of the endothelial cells composing the walls of these original sprouts. Such reservoirs of fluid as the subarachnoid spaces, the anterior chamber of the eye, the spaces of the internal ear (scala vestibuli and tympani) and the serous cavities (peritoneal and pleural) may be looked upon as belonging to the system of tissue spaces and as having developed from the dilatation and coalescence of smaller preexisting spaces in the mesenchyme. The fluid in the spaces of the central nervous system differs however from lymph and is drained, not by lymphatics, but by special absorbing structures—the arachnoid villi. Nor is the anterior chamber of the eye related to the lymphatics, but is drained through spaces in the pectinate ligament, and the aqueous humor differs in composition from lymph. Fluid is absorbed from the peritoneal cavity mainly via the blood capillaries. Solid particles (e.g., granules), on the other hand, are picked up by large phagocytic cells and conveyed into the lymph system, especially those of the diaphragm.

against the invasion of bacteria or other injurious agents travelling by the lymph paths. When an infection of a part—a finger for instance—lying distal to a gland occurs, the latter becomes inflamed as a result of the localization therein of some of the bacteria or their toxins carried in the lymph. The gland swarms with motile cells (phagocytes) which attack and destroy the invading organisms. In this way a barrier is raised against the passage of deleterious agents, particularly bacteria, into the blood stream. In the case of the limbs at any rate it appears that no material can pass from the tissues to the blood stream via the lymph without filtering through the lymph nodes. The effectiveness of the nodes

THE COMPOSITION OF LYMPH

The lymph of the peripheral (subcutaneous) lymph vessels and the fluid of the tissue spaces are closely similar in composition, and both resemble the blood plasma. They have, however, a protein content which is much lower than that of the blood fluid. Drinker found the protein content to vary under different conditions from 0.3 to 4.0 per cent in mammals. The higher figure, however, is unusual; concentrations between 0.5 and 0.7 per cent were found for human leg lymph. The protein of the tissue fluid (and so of the lymph) is derived, as we have seen, from the blood plasma. The proportion of albumin to globulin (2 to 1) is higher than in plasma as a

TABLE 4
Chemical composition of peripheral lymph (cervical) and blood plasma from the dog
(From Heim, 1933)

	PROTEIN (KJEL- DAHL)	NON- PROTEIN NITRO- GEN	UREA	URIC ACID	CREAT- ININE	SUGAR	AMINO ACIDS	CHLO- RIDES (AS NaCl)	PHOSPHORUS		CAL- CIUM
									Total	In- organic	
	<i>per cent</i>	<i>mg. per 100 cc.</i>	<i>mg. per 100 cc.</i>	<i>mg. per 100 cc.</i>	<i>mg. per 100 cc.</i>	<i>mg. per 100 cc.</i>	<i>mg. per 100 cc.</i>	<i>mg. per 100 cc.</i>	<i>mg. per 100 cc.</i>	<i>mg. per 100 cc.</i>	<i>mg. per 100 cc.</i>
Plasma:											
Average.....	6.18	32.6	21.7	Tr.*	1.37	23.0	4.90	678	22.0	5.6	11.70
Range.....	5.54–	21.1–	17.9–		1.22–	112.0–		649–	18.3–	4.4–	10.85–
	7.23	46.0	28.0		1.54	143.0		721	26.1	6.9	12.95
Lymph:											
Average.....	3.32	34.8	23.5	Tr.*	1.40	132.2	4.84	711	11.8	5.9	9.84
Range.....	1.38–	19.8–	19.8–		1.28–	107.0–		690–	10.2–	4.7–	8.93–
	4.57	45.4	33.0		1.49	144.0		730	13.7	7.3	10.84
Number of animals.....	16	10	7	3	7	16	1	7	6	3	11

* Tr. = trace.

as filters has been clearly demonstrated by Drinker and his associates. The popliteal and iliac lymph nodes of dogs were perfused with solutions containing virulent streptococci (250,000,000 colonies per cc.). After perfusion lasting for over an hour the fluid collected from the thoracic duct was found to be sterile. After the node itself has been attacked by the microorganisms it may then serve as a source from which the blood stream becomes infected. Though highly efficient as filters for bacteria the nodes appear to offer but slight hindrance to the passage of viruses. There is evidence that the lymph nodes contribute towards the body's defense in another way, namely, by the production of antibodies.

result of the freer passage of the former protein through the capillary wall. The fibrinogen concentration is very low. Lymph also contains prothrombin (p. 88). It clots slowly. Lymph contains large numbers of white cells, mostly lymphocytes, but very few red cells. The number of leucocytes varies from 1000 to 20,000 per cubic millimeter in thoracic duct lymph of the dog and averages 550 per cubic millimeter in peripheral lymph. Peripheral lymph contains from 300 to 13,000 erythrocytes per cubic millimeter. The lymph flowing from the thoracic duct, since it comes largely from the intestine and liver will vary in composition in accordance with the digestive processes. Its protein content is under

ordinary circumstances from 2 to 4.5 per cent. After a meal of fat the thoracic duct lymph is milky in appearance as a result of its high content in this material. The composition as well as the quantity of lymph varies considerably in different regions and under different experimental conditions which will be considered in the next section. Under ordinary conditions the pressure of the thoracic duct lymph is very low but if the duct is obstructed in the dog, a pressure of 15 cm. of water develops. The *rate of flow* along the human thoracic duct (as measured in cases of duct fistulae) is from 1 to 1.5 cc. per minute. Fat stained with Sudan IV appears in the thoracic duct lymph of man within about 1½ hr. after it has been swallowed. The composition of plasma and peripheral lymph (i.e., lymph in the subcutaneous vessels of the limbs or neck) are compared in table 4.

It will be noted that calcium and total phosphorus, which are in part bound with protein, are in lower concentration than in plasma; the other constituents with the exception of protein and amino acids are in higher concentration.

THE FORMATION OF LYMPH

After what has been said with regard to the forces concerned in the regulation of the fluid interchange between the capillaries and the tissues little need be added in explanation of lymph formation. The two processes are inter-related and similar in nature. Any condition which increases the outpouring of fluid from the capillaries into the tissues will tend to increase the flow of lymph. The lymph capillaries are much more permeable than the blood capillaries, and though the tissue spaces, i.e., the clefts between groups of tissue cells, are separated from the lymphatic system in an anatomical sense, the walls of the latter vessels are so permeable that they offer practically no barrier to either protein or crystalloids. It has been already stated that of the fluid which transudes from the blood at the arterial end of the capillary much of the water is reabsorbed from the venous end. The protein, however, passes into the lymph. The lymph capillary is therefore the special channel whereby protein is returned (in a round about way) to the blood. It is also concerned with the absorption of other colloids, or of particulate matter which may be introduced into the tissue spaces. It is an interesting fact that in the frog, in which the blood capillaries are much more permeable to protein than those of mammals the entire protein

of the plasma passes from the blood and back again to blood via the lymph system, some 50 times in 24 hours (fig. 10).

The mechanism governing the passage of tissue fluid into the lymph vessels is obscure, though the action of the pulse in the blood vessels of the part appears to play a part. McMaster and his associates have demonstrated the importance of a pulsatile flow in the vessels of the perfused rabbit's ear, in the spread of vital dyes through the tissues and in the formation and flow of lymph.

Conditions which increase the lymph flow

(1) INCREASE IN CAPILLARY PRESSURE AS A RESULT OF VENOUS OBSTRUCTION. Landis and Gibbon found that in man filtration from the capillaries showed a definite increase when the venous pressure rose above 12 or 15 cm. of water. The rate of filtration from the capillaries was directly proportional to the increase in venous pressure (fig. 12). At a given venous pressure the filtration rate increased rapidly at first but gradually slowed and finally ceased. This falling off in the filtration rate is ascribed to the rise in extracapillary pressure, due to the fluid accumulation, which opposes the hydrostatic pressure within the capillary.

Increased pressure in the veins of the portal area, as may be produced by obstructing the portal vein or the hepatic veins, causes increased filtration into the tissues of the abdominal viscera and a great increase in the volume of lymph flowing along the thoracic duct.

Increase in arterial pressure, on the other hand, does not increase filtration in animals until the pressure reaches around 300 mm. Hg.

(2) INCREASED PERMEABILITY OF THE CAPILLARY WALL. (a) *A rise in temperature* increases capillary permeability, raises the filtration rate and the flow of lymph.

(b) *Capillary poisons*. *Peptone* increases the flow of lymph from the thoracic duct probably as a result of its injurious effect upon the abdominal capillaries. The increased flow occurs after removal of the liver so injury to the vessels of this organ is not essential as was once believed (Markowitz and Mann). Other substances which increase lymph flow in this way are, extracts of strawberries, cray-fish, mussels and leeches; histamine and foreign proteins. Such materials are referred to by Heidenhain, as *lymphagogues of the first class*. Heidenhain held the view which is held no longer that the endothelium of the capillary possessed a true secretory function and

that it was stimulated to activity by lymphagogenic agents.

(c) *Reduced oxygen supply* to the tissues (oxygen want), probably through damage to the capillary endothelium.

(3) **HYPERTONIC SOLUTIONS.** The intravenous injection of a concentrated solution of glucose, sodium sulphate or sodium chloride causes an increased flow of lymph from the thoracic duct in the following manner. These substances in

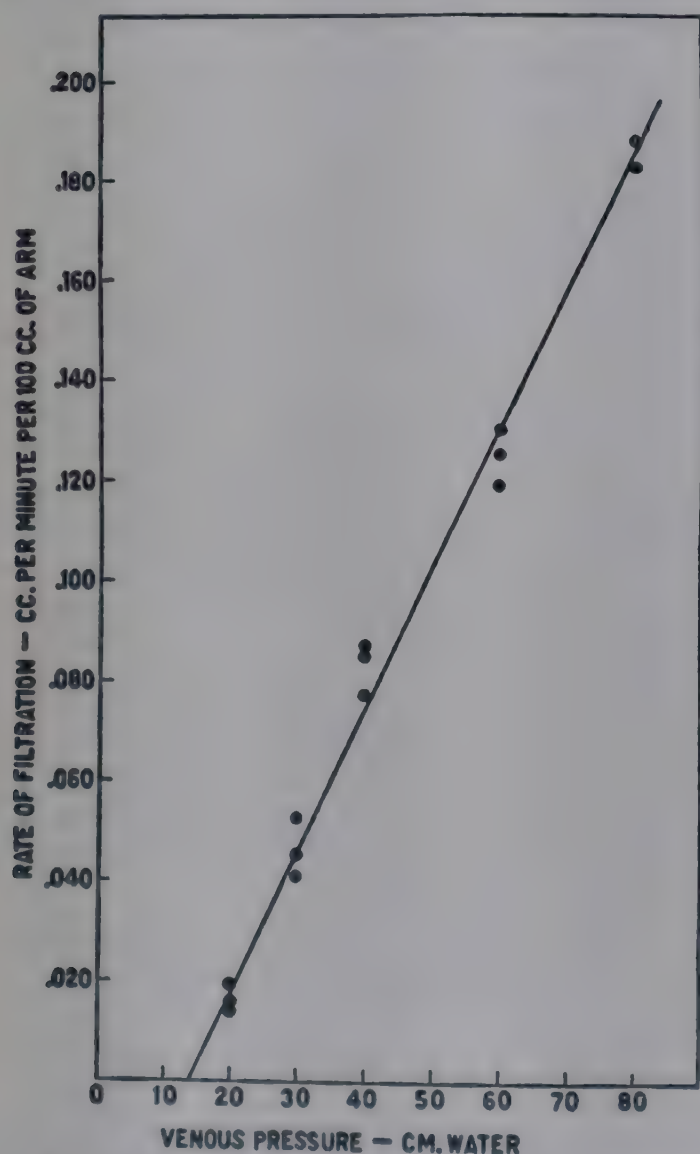


FIG. 12. Showing rates of filtration produced during 30 minutes by venous pressures between 20 and 80 cm. water (after Landis and Gibbon).

concentrated solution though they permeate the capillary wall exert an osmotic pressure until equilibrium between the extravascular and intravascular fluids is re-established. Fluid is "attracted" from the tissue spaces, particularly of the muscles and subcutaneous tissues of the limbs, which in consequence show a fall in volume; the brain shrinks. The removal of fluid may actually extend to the fluids within the cells which undergo shrinkage; and general desiccation of the tissues result (p. 17). The blood volume for

the time is greatly augmented, the excess fluid, for the most part being accommodated in the capacious capillary and venous areas of the abdomen. The viscera—liver, kidneys, spleen and intestines—increase in volume, due to the distension of their vascular beds, and a great outpouring of fluid occurs, which swells the volume of lymph in the thoracic duct. In this way these substances produce a redistribution of fluid. Since the water-logged tissues eventually give up the extra fluid for excretion the body suffers a net loss.

The injection of isotonic saline will also increase the lymph flow since the plasma colloids are diluted thereby and the filtration through the capillary is increased. Substances which increase the flow of lymph in the manner described in this section are sometimes spoken of as *lymphagogues of the second class*.

The effect which hypertonic solutions have upon the movement of tissue fluids had extensive application during the first World War. Sir A. E. Wright introduced the practice of packing wounds with salt crystals or irrigating them with a hypertonic salt solution. This causes an outward flow of lymph and tissue fluid, which results in the mechanical removal of the bacteria and their toxins from the tissues bordering the wound.

(4) **INCREASED FUNCTIONAL ACTIVITY.** When a gland or muscle enters into activity an increase in lymph flow occurs which starts a little after the commencement of the secretory or contractile response, but is nearly synchronous with the increased metabolism resulting from the activity. The increased flow is ascribed to (a) formation of metabolites which increase the osmotic pressure of the tissue fluids and so "attract" more fluid from the vessels (b) vasodilation and increased capillary pressure.

During rest the flow along the lymph vessels of the muscles and subcutaneous tissues is slight, and the protein content of the lymph is high. During activity the protein concentrations fall since less transuded water undergoes reabsorption into the blood and more is carried away by the lymph channels. The contracting muscles exert a pumping effect upon the lymph, driving it along the vessels.

(5) **MASSAGE AND PASSIVE MOVEMENT** act to a certain extent like muscular activity. They augment the blood flow and capillary pressure and so increase lymph formation. The manipulations and movements of the muscles serve to propel the lymph along the lymphatic channels.

EDEMA (SEE ALSO P. 406)

Edema is the term applied to an excessive accumulation of fluids in the tissue spaces, and is due to a disturbance in the mechanisms of fluid interchange, which have been considered in the preceding pages.² Instead of there being a perfect balance struck between the inward and outward flow of fluid through the capillary membrane absorption is exceeded by transudation. The particular factor or factors of the mechanism that are disordered are not always clear, and a satisfactory explanation of all forms of edema cannot be given. But from previous discussions it is evident that edema may arise from (1) Reduction in the osmotic pressure of the plasma, i.e., in protein concentration. (2) General or localized changes in capillary blood pressure. (3) Increased permeability of the capillary membrane. (4) Obstruction of the lymph channels. There is a tendency for edema to reach a certain degree and then become stationary provided the conditions producing it remain constant, for as we have seen, when the tissue fluid pressure reaches a critical level its opposition to the force driving fluid from the vessels prevents further transudation.

Since edema is only a symptom of some primary condition it may have a variety of causes, according to the particular disease with which it is associated.

(1) *Cardiac edema.* This is due mainly to the slowing of the peripheral blood flow and the resulting rise in capillary pressure. The increased venous pressure and the distension of vessels in the capillary areas will be greatest in dependent parts of the body, and it is here that the edema of cardiac failure usually first makes its appearance.

² When the subcutaneous tissues are involved these appear swollen, and leave the imprint of the thumb when it is pressed into the skin (pitting). Dropsy (hydrops) is an old-fashioned term which is applied to edema as defined above or to a free collection of fluid within one of the body cavities, e.g., the thorax or the abdomen. *Hydrothorax* is also applied to the former of these conditions and *ascites* to the latter. *Anasarca* is a more or less generalized edema involving the subcutaneous tissues.

It is important to remember that the term edema applies to a gross collection of extravascular fluid. The bulk of tissue fluid fluctuates widely in health, and in pathological states may be very considerably increased before the increase is evident clinically. When, for example, a normal person stands for a time the extravascular fluid of the legs increases; and the immersion of a limb in a hot bath hastens the rate at which fluid transudes from the vessels—the limb volume rises as a result, largely, of fluid accumulation in the tissues. Drury and Jones found that edema appeared when the increase in fluid increased the volume of the leg by 8 per cent.

Collection of fluid in the peritoneal or the pleural cavity also commonly occurs. Edema commences when the capillary blood pressure rises to within 2 mm. Hg of the osmotic pressure of the plasma. In some cases, reduction in plasma protein concentration is also a factor in cardiac edema.

Damage and increased permeability of the capillary membrane due to deficiency in the oxygen supply to the tissues (stagnant type of anoxia, p. 359) may be a contributory cause.

(2) *Mechanical obstruction of veins.* When the main veins leading from a part are obstructed by new growth, fibrous tissue, as in cirrhosis of the liver, thrombosis, etc., increased transudation of fluid occurs. This is due in part to the rise in intracapillary pressure but the permeability of the capillary wall is also increased as a result of the impaired blood supply or, as in the case of new growth, probably to the production of toxic substances as well.

(3) *Edema due to renal disease.* In chronic glomerulo-nephritis and in nephrosis the edema is due to the reduction in the concentration of the plasma proteins and so of the osmotic pressure of the blood (see p. 23). In acute nephritis the capillary wall is damaged and its permeability increased, protein escapes in excessive amounts into the tissues, so the edema fluid has a relatively high protein concentration.

(4) *Inflammatory edema.* In this type several factors combine to produce the fluid infiltration of the tissues. Increased capillary pressure occurs, due to dilatation of the vessels and local slowing of the blood stream (p. 114) as well as to thrombosis and obstruction of the returning veins. The lymphatics for a variable distance from the inflammatory area are obstructed as well. The capillary walls are also seriously damaged by the bacterial toxin or other injurious agent, so that a fluid with a high protein content escapes from the vessels. The edema is localized to an area of varying extent surrounding the injured site.

(5) *Giant edema.* This is a localized non-inflammatory edema which comes on with great rapidity and involves the loose areolar tissue in such regions as the hands, face, genitalia or larynx. It occasionally runs in families. Little is known definitely regarding the mode of its production. A histamine-like substance liberated at the site of the edema is apparently the immediate cause (p. 269). The remote exciting cause is frequently a foreign protein consumed in the diet which apparently gains access to the blood stream in a more or less unchanged state, for the attack often follows a particular food to which the subject is sus-

ceptible, and is sometimes accompanied by gastrointestinal disturbances. The effects are therefore of an anaphylactic nature and constitute one type of allergy. This type, also termed *angioneurotic edema*, is allied to the very localized edemas which constitute the condition known as urticaria and which as suggested by Lewis are due to the liberation of a histamine-like substance in the skin.

(6) *Edema due to malnutrition or to toxic substances.* Edema may occur in the anemias or in conditions in which the general nutrition of the body suffers. When the diet is deficient in vitamins, or there is too little fat or protein in the diet edema may occur, as in beriberi, scurvy, "war edema" or in the faulty nutrition of infants. In animals edematous conditions have actually been induced by general underfeeding, or by a diet deficient in fat and in fat soluble vitamins, or by one deficient in protein alone. The factors responsible for the increased transudation in these cases are not always clear, but in others there is a marked lowering of plasma protein which alone is sufficient to account for the development of the condition. Changes in the capillary membrane as a result of impaired nutrition, or due to the direct action of toxic substances are indicated in some cases.

Certain chemical substances such as arsenic, salts of heavy metals, and the toxins of certain infectious diseases, such as diphtheria, acute nephritis, etc., are known to act as capillary poisons and apparently cause edema in this way. An interesting type of a toxic edema is that which may be produced in animals by the injection of hematoporphyrin (p. 46). This substance appears to sensitize the tissues towards light rays, and the edema occurs only after exposure.

Histamine causes local edema at the point of injection by inducing capillary dilatation and increased permeability of the membrane (p. 269).

(7) *Edema due to lymphatic obstruction.* Obstruction to the outflow of lymph from the tissue spaces may cause pronounced edema, even though the venous channels and the capillary vessels are unaffected. Edema of this nature is readily produced in frogs by compression of the lymph channels alone. It is more difficult to produce edema in this way in higher animals but if the obstruction is complete edema also occurs in these also. Edema of this nature is seen in infections with the filarial parasite which finds its way into the lymph vessels of the limbs and blocks their lumen with the production of the condition known as elephantiasis. The pleural cavities depend for the absorption of a fluid upon the lymph channels, and accumulations of fluid may occur here as a result of lymphatic obstruction. The edema associated with carcinoma is due chiefly to the filling of the lymphatic channels with cords of cancer cells as well as to venous obstruction caused by the pressure of the growth. The "milk leg" of the puerperium is in part due to lymphatic obstruction.

(8) *Heat edema.* The effect of heat upon capillary permeability has been mentioned (p. 29). Excessive heat may actually lead to edema in man. It occurs in the tropics and occasionally in temperate (so-called) zones during an intense heat wave. Increase in blood volume, enlargement of the filtering surface as a result of the opening up of fresh capillaries and the rise in capillary pressure incident to the dilatation of capillaries previously patent, are also factors in the production of this type of edema.

CHAPTER V

TRANSFUSION

The materials employed for restoring the blood volume to normal are; (1) *Whole blood*, (2) *plasma or serum*, (3) *solutions of colloids*, e.g., gum acacia, isinglass etc., (4) *solutions of crystalloids*, e.g., saline or glucose solutions.

(1) WHOLE BLOOD¹

Theoretically, whole human blood is, of course, the ideal transfusion fluid. The improvements and simplification of technique in recent years and the advance in knowledge of blood incompatibilities have made blood transfusion immeasurably safer, and rendered it available under circumstances which hitherto would have been insuperable. It is not only in cases of emergency such as severe hemorrhage or wound shock, but in several other conditions that it is used today. Below are listed some of the conditions in which it is employed.

Hemorrhage.

Hemorrhagic diseases, e.g., hemophilia, purpura hemorrhagica, anemias and leucemias.

Shock (wounds, burns).

Malnutrition in infants, marasmus, acute intoxications.

Septic conditions, septicemias.

The red cells of the transfused blood survive and carry out their functions for several days after their injection. On this account whole blood is greatly superior to any other transfusion fluid

¹ Within recent years stored blood (or plasma) is being used to an ever increasing extent. Blood collected from the dead has been employed in Russia, but cadaver blood for obvious reasons, has not found general favor. Placental blood or blood removed by venesection from cases of congestive heart failure may be employed, but the blood of healthy donors is preferable. The blood is preserved at a temperature of around 1°C. after dilution with a citrate-dextrose mixture in the proportions of 5 parts of blood, 1 part of 3.2% citrate solution and 6.5 parts of 5.4% dextrose solution. Kept in this way blood remains suitable for transfusion for twenty days, perhaps longer. It was found, however, by Belk and Barnes that the survival time of the red cells after transfusion was very short (24-48 hours) if the blood had been stored for more than 2 or 3 days. Others find, however, that most of the cells of the preserved blood survive for a longer period than this. These so-called *blood banks* have the advantage that a quantity of blood already prepared for transfusion can be obtained at a moment's notice. But there is also the great disadvantage that any blood not used within ten days or so must be discarded.

in any condition in which the respiratory area of the blood has been greatly reduced, e.g., very severe hemorrhage or hemorrhage in an anemic person, CO poisoning, etc. It is also more effective in traumatic shock than plasma, serum or other blood substitutes. According to Ashby, from 60 to 80 per cent of the donated cells live for over 30 days. Fifty per cent were detectable in some cases after more than 45 days. The use of blood as a transfusion fluid, nevertheless, is hedged about by hazards both to the recipient and to some extent to the donor. On this account it is a suitable method only when adequate facilities for guarding against these dangers are available, otherwise some blood substitute will have to be resorted to. The safeguards which must be taken are:

(a) The donor must be healthy. Several cases have been reported of disease having been transmitted by the transfused blood. Syphilis malaria and acute diseases have been reported to have followed blood transfusion. In some instances the transmission in the transfused blood of a particular foreign protein of dietary origin, to which the recipient but not the donor is sensitive, has caused an allergic reaction.

(b) A too rapid transfusion of blood is dangerous, especially in children or undersized persons, for the sudden increase in circulating fluid may cause serious embarrassment to the right side of the heart. In an adult, the usual transfusion rate is from 100 to 200 cc. per hour, but one of 20 cc. or less causes little cardiovascular effect, even though the blood volume is considerably increased. At higher rates, the venous pressure rises and the cardiac output increases. Rapid infusions of fluid into animals causes death from cardiac failure, preceded by an inordinate rise in venous pressure and pulmonary edema. The total quantity injected varies according to circumstances and the size of the patient, from about 500 to 1500 cc. or more.

(c) An ever present potential danger is that of incompatibility. The donor's blood must always be tested for its compatibility with the blood of the recipient. Normal plasma contains substances which have the power to cause the clumping together (agglutination) and subsequent disintegration (hemolysis) of the foreign corpuscles of another

species. Agglutination may also result when the bloods of two human individuals are mixed. The bloods are then said to be incompatible and transfusion under such circumstances will lead to very serious if not fatal results (p. 35).

THE BLOOD GROUPS

As a result of the work of several investigators in the early years of this century, notably that of Landsteiner, of Jansky and of Moss, it has been established that the blood of any person falls into one or other of four well defined groups, according to its agglutinating reactions. These groups were originally designated by the Roman

TABLE 5
Jansky's classification of blood groups

CORPUSCLES	SERUM			
	O	A	B	AB
O (I)	-	-	-	-
A (II)	+	-	+	-
B (III)	+	+	-	-
AB (IV)	+	+	+	-

+ means agglutination; - means no agglutination.

Group O. The serum of which agglutinates the corpuscles of the other three groups. The corpuscles of this group are not agglutinated by any serum.

Group A. The serum agglutinates the corpuscles of Groups B and AB, but not those of Groups O and A. The corpuscles are agglutinated by the serum of Groups O or B, but not by that of Groups A and AB.

Group B. The serum agglutinates the cells of Groups A and AB, but not those of Groups O and B. The corpuscles are agglutinated by the serum of Groups O or A, but not by that of Groups B and AB.

Group AB. The serum of this group does not agglutinate any corpuscles. The corpuscles are agglutinated by the serum of all other Groups.

numerals I, II, III and IV, respectively, but are now referred to by the letters O, A, B and AB (see p. 36). According to the classification of Jansky (1907) which is most commonly employed, and which out of respect for its priority has been recommended by a committee of the American Bacteriological Society, the groups exhibit the reactions shown in table 5.

About 43 per cent of all individuals of Western races belong to Group O and 40 per cent to Group A. Thirteen per cent and 4 per cent belong to Groups B and AB, respectively.

The alternative classification of Moss (1910) is sometimes employed. In this, Group O corre-

sponds to Jansky's Group AB, and Group AB to Jansky's Group O.

Consultation with the table will show that the serum of Group AB (vertical row on extreme right) is compatible with the corpuscles of all the other groups, i.e., no agglutination of the corpuscles of any donor should occur when the recipient belongs to this group. It will be noted however, that the cells of Group AB (lowest horizontal row) are agglutinated by the sera of all the other groups when tested outside the body. It might therefore be thought that this reaction could occur in the blood of the recipient but as a matter of fact, when a patient belonging to Group AB is transfused with the blood of any other group, agglutination of his (patient's) corpuscles does not usually occur. The reason for this is not clear, unless it is that the serum of the injected blood is so highly diluted by the patient's serum. It is said however, that if the donor's serum be diluted to the same degree as occurs when it is transfused and is then mixed with the cells of group AB outside the body, agglutination does occur. Whatever the explanation, the fact remains that the reaction of the donor's corpuscles to the serum of the recipient is the important factor to consider, and that the agglutinating property of the donor's serum is not generally evident. On this account members of Group AB are sometimes spoken of as "universal recipients."

It will be seen from the table that the corpuscles of Group O (uppermost horizontal row) are not agglutinated by any serum. Members of this group are therefore called "universal donors" since agglutination does not, as a rule, occur when this blood is transfused into a member of any of the other groups.

The terms "universal donor" and "universal recipient" though in general use are dangerously misleading. Severe and even fatal reactions may occasionally result from the transfusion of blood of group O into a subject of one of the other groups. Similarly, it cannot be taken for granted that a subject of group AB can be transfused with impunity with the blood from any of the other groups. Such procedures are especially hazardous in the case of children, probably for the reason that they are transfused with relatively large quantities of blood than are adults; the donor's blood, in consequence, is in relatively high concentration in the recipient's blood stream. Therefore, blood of the same group to which the recipient belongs should always be employed, unless it

unobtainable and the emergency does not brook delay.

Determination of the group to which a particular blood sample belongs

In order to determine the particular group to which a given sample of blood belongs, it is not necessary to have sera of each group, but only of Groups A and B. Sealed tubes containing high titer sera of these two groups are kept on hand for testing purposes. Reference to tables 5 and 6 and to figure 13 will show the reason for this. If a diluted specimen of the unknown blood is agglutinated neither by Group A or Group B serum, it must belong to Group O. If it reacts to Group B serum but not to Group A, it must belong to Group A, and similarly, if it reacts to Group A but not to Group B, it belongs to Group B. If it is agglutinated by both test sera, it belongs to Group AB. To perform the test a

TABLE 6
Reaction of red cells of unknown

UNKNOWN BLOOD	GROUP A SERUM	GROUP B SERUM	GROUP TO WHICH SAMPLE IS ASSIGNED
X	-	-	O
X	-	+	A
X	+	-	B
X	+	+	AB

+ = agglutination; - = no agglutination.

drop each of Group A and Group B sera are placed side by side upon a white opal glass tile which has been slightly warmed. A specimen of blood from the person whose blood group is being determined is mixed with a 0.9 per cent solution of sodium chloride to make a 2 to 5 dilution. A drop of the diluted blood is added to each sample of test serum.

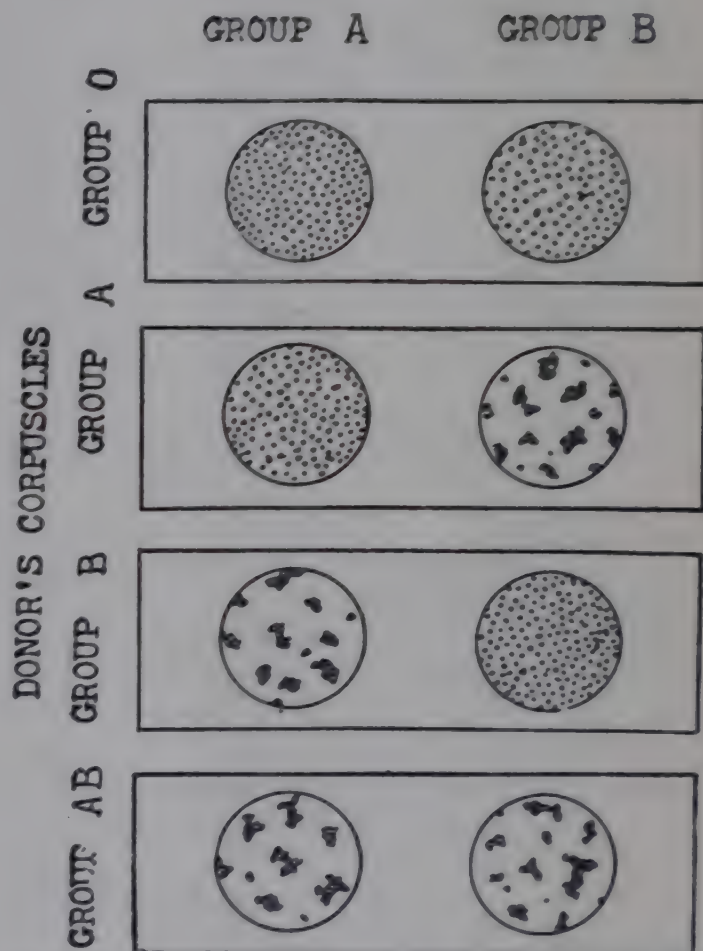
Agglutination, if it occurs, is usually visible under the microscope within a few minutes or may be seen with the naked eye, the clumped corpuscles appearing like grains of cayenne pepper upon a clear fluid. The reaction, however, may be delayed for as long as 20 minutes. In the absence of agglutination the fluid remains uniformly pink. Lists of donors, classified in respect to the groups to which they belong, are usually kept in large clinics so that the appropriate blood can be obtained quickly in an emergency. Cross or direct matching also should be carried out as an additional check. A diluted specimen of the recipient's blood is mixed with a sample of the

donor's serum, and a similar sample of the donor's blood with the patient's serum. The mixtures are observed microscopically for agglutination.

The effects of the transfusion of incompatible blood

The most urgent symptoms develop. Among these are tingling pains shooting through the body, severe lumbar pain, precordial distress, cyanosis, rapid thready pulse and other manifestations of severe collapse which frequently end fatally. Hemoglobin

TEST SERA



DONOR'S CORPUSCLES GROUP IV (AB) GROUP III (B) GROUP II (A) GROUP I (O) TEST SERA GROUP II (A) GROUP III (B)

FIG. 13. Showing the effects of the sera of groups A and B upon the corpuscles of the several blood groups.

appears in the urine almost invariably. Symptoms are due, in part at least, to the mechanical effect of the agglutinated corpuscles, which cause the blockage of small vessels in vital regions. Later, hemolysis of the agglutinated cells occurs. In fatal cases the tubules of the kidneys have been found blocked with hematin produced by the action of the acid urine upon the hemoglobin liberated from the broken down erythrocytes. Suppression of urine preceded death. When an accident, due to the transfusion of incompatible blood, threatens, an attempt is made to prevent the deposition of pigment in the tubules by rendering the urine alkaline. In some cases the symptoms are

of an anaphylactic nature due to the protein of the foreign serum rather than to any agglutinating reaction, and occur after the later transfusions of a series from the same donor. Minor reactions which are not easy to explain sometimes occur even when the bloods appear by the usual tests to be compatible. (See also p. 37).

TABLE 7*
General table of group inheritance

PARENTAL COMBINATION	NUM- BER OF FAMI- LIES	NUMBER OF CHILDREN IN EACH GROUP			
		I (O)	II (A)	III(B)	IV (AB)
O × O	1,192	2,630	15	2	
A × A	1,256	476	2,364	1	1
O × A	2,535	2,256	3,021	18	9
B × B	293	126		532	1
O × B	997	958	11	1,230	1
A × B	1,104	401	791	641	580
O × AB	465	38	571	525	34
A × AB	481	21	525	253	307
B × AB	327	13	121	306	159
AB × AB	67		39	42	70
Total	8,717	6,919	7,458	3,550	1,162
			19,089		

* From Lattes, L., Individuality of the Blood, Oxford Medical Publications, 1932.
The exceptions to the rule are shown in heavy type. They are probably due to illegitimacy.

TABLE 7½
Showing the presence in the various groups of agglutinogens and agglutinins (Tansky)

GROUP	CELLS CONTAIN ISO-AGGLUTINOGENS	SERUM CONTAINS ISO-AGGLUTININS
O	O (neither)	α and β
A	A	β
B	B	α
AB	A and B	o (neither)

Agglutination occurs only when corresponding iso-agglutinins and iso-agglutinogens are brought into contact, as would be the case were Group B serum mixed with Group A cells. Obviously such a combination does not exist in the blood of any individual, otherwise auto-agglutination would occur.

Theory of blood grouping

Landsteiner postulated the existence of two specific substances in serum which he called *iso-agglutinins*, and two substances in the corpuscles which he termed *iso-agglutinogens*. The former may be represented by the Greek letters α and β; the latter by the capitals A and B. A given serum might contain one, both or

neither iso-agglutinin. Similarly the corpuscles may contain one, both or neither iso-agglutinin (table 7½). In order for agglutination to occur when two bloods are mixed α must be present with A (αA) or β with B (βB). If o be used to represent the absence of the two iso-agglutinins and O the absence of the two iso-agglutinogens then the four groups may be designated as follows:

Group O. The corpuscles have no iso-agglutinin (O); the serum has α and β iso-agglutinins. This group may therefore be designated Oαβ. Its corpuscles obviously cannot be agglutinated by any serum but its serum will agglutinate any corpuscles containing A or B, i.e., the corpuscles of any of the other groups.
Group A. Corpuscles have A; serum has β. This group may therefore be represented by Aβ. Its corpuscles are agglutinated by any serum containing α; its serum agglutinates corpuscles containing B.
Group B. Corpuscles have B and serum has α. The group is represented by Bα. The corpuscles are agglutinated by a serum containing β and the serum agglutinates corpuscles containing A.
Group AB. Corpuscles have A and B but serum has no iso-agglutinins. The group is represented by ABo. Obviously the corpuscles are agglutinated by any of the other sera, but the serum of this group will not agglutinate the corpuscles of any other group.

It is owing to the confusion which has arisen from the existence of two classifications, Jansky and Moss, that the system has been adopted whereby the blood groups are referred to by the letters indicating their serological characteristics, namely Oαβ, AB etc., or simply by letters showing the characteristics of the corpuscles, that is, O, A, B and AB.

Hereditary transmission of the blood groups

It is sometimes thought that close relatives must have compatible bloods, and that consequently a child could be transfused without harm with the mother's blood. The placenta, however, offers a barrier to the passage of the serological characters of the maternal blood into the blood of the fetus. It is true, on the other hand, that the iso-agglutinins are established much later after birth than the iso-agglutinogens, and may be in very low concentration in the new-born (whose blood would therefore correspond to Group AB). It has therefore been suggested that the mother's blood no matter to what group it belonged would not undergo agglutination when transfused into the baby; but this is a decidedly dangerous assumption, for iso-agglutinins are not always in low concentration at birth.
The blood once established in its group remains unchanged throughout life. Even after a large number of transfusions, blood retains its original serological characters.

The agglutinability of the corpuscles of the different groups is inherited as independent pairs of factors. Group A is due to the inheritance of iso-agglutinin A and iso-agglutinin β . The iso-agglutinin is a dominant factor, the iso-agglutinin is recessive. We may therefore refer to the character of this group as A. Group B depends upon the inheritance of the iso-agglutinin B. The character of this group may be referred to therefore as B.

There are therefore two dominant factors, A and B, and two recessive factors, α and β . The letter O is used to represent the absence of both dominants A and B. Since this means that the recessives alone are present, O will simply stand for the recessive characters. If neither parent possesses a dominant factor, i.e., they both belong to Group O (I), the child obviously cannot receive either A or B and so must also belong to Group O. If one parent possess only one dominant, say A, the other only B, then the child may receive A from one and B from the other and so belong to Group AB (IV). But since the parents must also each possess a hidden (recessive) factor, the child may inherit α from one and β from the other and so belong to Group O (I). Or it may receive an A or a B together with a β or an α , and so belong to Group A (II) or B (III) respectively. Again, if one parent is an AB, the other A or B, the child could not be of Group O since it would under any circumstances receive at least one dominant factor. It might belong to Group A, B or AB, depending upon chance. The possible parental combinations and the proportion of the children which will fall into each group for any given combination are shown in table 7 from Lattes.

Subgroups. The main blood group A is made up of the subgroups A_1 and A_2 , and the main group AB of the subgroups A_1B and A_2B . This is because the cells of both these groups may contain one or other of two types of agglutinogens which have been designated A_1 and A_2 . About 75 per cent of persons belonging to group A are included in subgroup A_1 and about 20 per cent in subgroup A_2 . In rare instances, the agglutinin α_2 is present in the plasmas of subgroups A_1 and A_1B and agglutinin α_1 in the plasmas of subgroups A_2 and A_2B . The main group O (universal donor, so-called) may also, though very rarely, contain the α_1 agglutinin. Should the plasma of a donor contain α_1 agglutinin (anti- A_1) in high titer and the recipient belong to subgroup A_1 or A_1B a reaction will occur. Similarly, α_2 plasma will be incompatible with A_2 or A_2B cells. The subgroups and the distribution of the agglutinogens and agglutinins are shown in the table below.

The Rh factor. Landsteiner and Wiener reported the discovery of an agglutinin which they named the *Rh factor*, because it is present in

Rhesus monkey blood as well as in human blood in 85 per cent of white persons.² Should a donor whose blood contains the Rh factor be transfused into a patient whose blood does not contain it, an anti-Rh agglutinin is developed in the recipient's blood. The anti-Rh agglutinin develops within 12 days following the transfusion, and if a second transfusion should be given to such a patient after this period a hemolytic reaction due to the action of the anti-Rh factor results. A hemolytic reaction caused by this factor may follow a single transfusion in pregnant women or post-partum, which is thought to be due to the anti-Rh agglutinin formed in the mother's blood as a result of the blood of the fetus containing the Rh factor inherited from the father.

BLOOD GROUPS	AGGLUTINOGENS (IN CELLS)	AGGLUTININS (IN PLASMA)
O	None	α and β (rarely α_1)
A $\left\{ \begin{matrix} A_1 \\ A_2 \end{matrix} \right.$	A_1	β (rarely α_2)
B	A_2	β (rarely α_1)
AB $\left\{ \begin{matrix} A_1 \\ A_2 \end{matrix} \right.$	B	α
	A_1 and B	None (rarely α_2)
	A_2 and B	None (rarely α_1)

A fatal blood disorder of the new-born, known as *erythroblastosis fetalis*, is believed to be due to the production of an anti-Rh agglutinin in the mother's blood which crosses the placental barrier and causes destruction of the red cells of the fetus whose blood, in 90 per cent of cases of this disease, is Rh positive.

Other agglutinogens, designated M and N, have been discovered more recently. Approximately 45 per cent of white persons have both M and N agglutinogens. The remaining 55 per cent have either M or N, most frequently the former. The plasma normally contains no antibodies (agglutinins) for these factors, but an anti-M or an anti-N agglutinin may develop in the blood of the recipient if he has been transfused repeatedly with blood from a donor belonging to the other subgroup. A reaction is not likely to occur, however, since the agglutinin is rarely, if ever, of sufficiently high titer to cause agglutination.

(2) HUMAN SERUM AND PLASMA

Many of the drawbacks inherent in the use of whole blood for transfusion are obviated by substituting human serum or plasma. These blood

² This percentage does not hold true for certain races, e.g. American Indians.

derivatives when pooled from a number of donors can be transfused indiscriminately without regard for the blood groups. Furthermore, liquid plasma or serum if collected under strictly sterile conditions can be stored under refrigeration for an indefinite period. Plasma kept in the frozen state is highly recommended by Strumia and McGraw as being safer than storage in liquid form. Plasma or serum dried *in vacuo* from the frozen state by the *desivac process* of Flosdorf, Stokes and Mudd is the preparation *par excellence*, especially for use in the armed services. It can be stored without refrigeration, is easily transported and the dangers of bacterial contamination or of deterioration are at a minimum. When required for use, distilled water, equal in volume to that which had been removed in the drying process, is added.

(3) SOLUTIONS OF COLLOIDS

The limited availability of whole human blood or of its derivatives, plasma or serum, has inspired a search for a blood substitute which would resemble as closely as possible the physical properties of plasma. The requirements of an artificial transfusion material are several. (a) The molecules (or particles) of the substance must be of such a size that its solution will not leave the circulation too freely. (b) The solution must have an osmotic pressure and a viscosity approaching as closely as possible these properties of whole blood: such qualifications depend upon molecular size and shape. (c) It should be isotonic with the contents of the corpuscles. (d) It must, of course, be non-toxic and innocuous in every respect. (e) It should not hinder plasma protein production. In addition, the material should be readily available in large quantities, preferably cheap, capable of being sterilized by simple means, and of being quickly prepared for use. Provided a material is suitable for transfusion in the foregoing respects there appears to be no valid objection to the use of some fluid other than blood or its derivatives to fill the vessels after hemorrhage. The properties which render a fluid suitable for transfusion are physical rather than chemical. Blood apparently possesses no advantage by virtue of any biochemical characteristics which it possesses.

Gum acacia in a 6 per cent solution in saline was introduced by Bayliss as a transfusion fluid during the first World War and proved highly successful. The osmotic pressure and viscosity of this solution closely resemble those of plasma.

The molecules of *gum acacia* aggregate into particles comparable in size to those of the plasma proteins and do not escape freely through the capillary membrane.

However, experience since the first world war has revealed some undesirable features of *gum acacia*. *Gum acacia* is a polysaccharide which the body cannot metabolize. It, like other foreign materials which cannot be disposed of in other ways, is taken up by the reticulo-endothelial elements of the liver and elsewhere. The liver may become greatly enlarged after repeated transfusions with this material and sometimes shows areas of necrosis. The hepatic function of producing plasma protein is seriously depressed; the concentration of protein in the plasma is lowered following large transfusions of *gum acacia* and may remain below normal for a considerable time after this blood substitute has been administered.

Isinglass (collagen prepared from the swim-bladders of certain species of fish, e.g., sturgeon, hake, etc.) has been advocated by Taylor and Waters, in a concentration of 6 per cent in physiological saline, as a blood substitute. Such a solution fulfills the requirements of a blood substitute listed above. It has been used clinically and offers much promise as a blood substitute. It is free from anaphylactic or pyrogenic reactions. The molecular weight of *isinglass*, after autoclaving, is between 18,000 and 30,000.

Animal gelatin, which is closely similar to *isinglass* chemically, has been used clinically with satisfactory results.

Pectin, a hemicellulose (consisting of partially methylated galacturonic acid anhydride units) which is obtained from citrus and other fruits and used domestically as a jellying agent, has been employed by Hartman and his associates.

Other transfusion materials which are being subjected to animal experimentation are *hemoglobin-Ringer* solution, under investigation by Amberson and his colleagues, and *human and beef albumin* by Cohn, Janeway and associates. The reader interested in this subject is referred to the original papers.

(4) SOLUTIONS OF CRYSTALLOIDS

The small molecules of salt or of glucose pass freely through the capillary wall. They exert a negligible osmotic effect; the injected fluid is therefore not retained in the circulation. For this reason such fluids though capable of raising the blood pressure temporarily are quite unable

to maintain it for any considerable length of time. Indeed they may do serious harm, for the transfused fluid as it leaks into the tissues carries plasma protein with it. This is particularly likely to occur in the case of saline. Transudation of fluid into the tissue of the lung—pulmonary edema—may result. When, on the other hand, dehydration of the tissues and loss of blood *water*, as shown by the concentration of the plasma proteins, are prominent features, then the subcu-

taneous or intravenous injection of saline (with the addition of glucose) or water by mouth, would appear, from physiological principles, to be a logical procedure. In the dehydration resulting from chloride depletion (p. 18) sodium chloride is clearly indicated. A solution of this salt serves not only to supply fluid but to replenish the base the loss of which is such an important factor in the development of the dehydrated state.

CHAPTER VI

HEMOGLOBIN

Hemoglobin is the coloring matter of the erythrocytes, and the chief function of the red cell is to store this pigment and carry it around the circulation. About 10 grams of hemoglobin pass through the lungs per second. It takes up a comparatively large load of oxygen which it carries to the tissues. One hundred cubic centimeters of water at the temperature of the body and exposed to an oxygen pressure of 100 mm. Hg absorbs a third of a cubic centimeter of the gas. One hundred cubic centimeters of blood, on the other hand, at the same temperature and pressure will take up about 20.0 cc.,—that is, 60 times more. The difference is due to the hemoglobin. The total amount of blood in the human body will hold approximately 1200 cc. of oxygen (200 cc. per liter of blood). This quantity of oxygen is used by the tissues in 5 minutes or so during rest and in a fraction of a minute during muscular exertion. In the absence of hemoglobin, the entire duty for the carriage of oxygen would have to be performed by the plasma, and in order that this should be able to absorb the necessary amount of gas, it would have to be increased at least 60 times in amount. As pointed out by Barcroft, the circulating fluid, instead of being about 6 liters or $\frac{1}{11}$ of the body weight, would then need to be over 350 liters. That is, more than five times the bulk of the solid tissues.

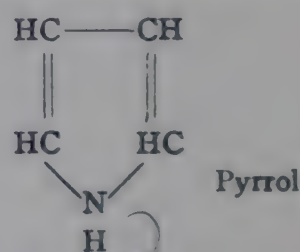
THE CHEMICAL CONSTITUTION OF HEMOGLOBIN. THE "STONES" FROM WHICH ITS MOLECULE IS BUILT

Hemoglobin is a conjugated protein consisting of an iron-containing pigment portion combined with a protein of the histone class called *globin*. The hemoglobin complex when its globin is in the natural state, forms a loose combination with oxygen (oxygenation)—the iron being in the ferrous state (Fe^{++}). Under certain abnormal conditions it forms a stable compound with oxygen (oxidation, i.e., the production of a true oxide)—the iron being in the ferric state (Fe^{+++}). A more detailed consideration of hemoglobin structure follows.

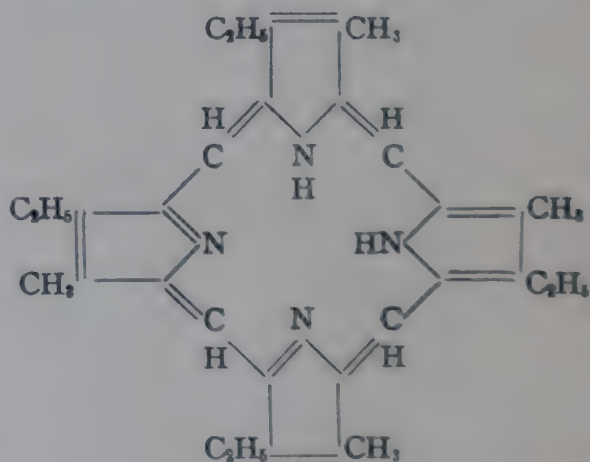
PORPHYRINS are pigments which either alone or as the basis of more complex compounds are found throughout plant and animal life from the highest

to the lowest forms. A porphyrin is the pigment basis of chlorophyll—the green coloring matter of plants. One is found as a brown pigment in the shells of many eggs, and also in the dark line running down the back of the earthworm. On the other hand, when conjugated with other substances porphyrins are the basis of the blood and tissue pigments of various animals.

The porphyrin molecule is constituted of four pyrrol nuclei. The pyrrol nucleus has the following structure:



Four of these rings joined together constitute porphyrin. The manner in which the rings are connected may be seen in the following formula.

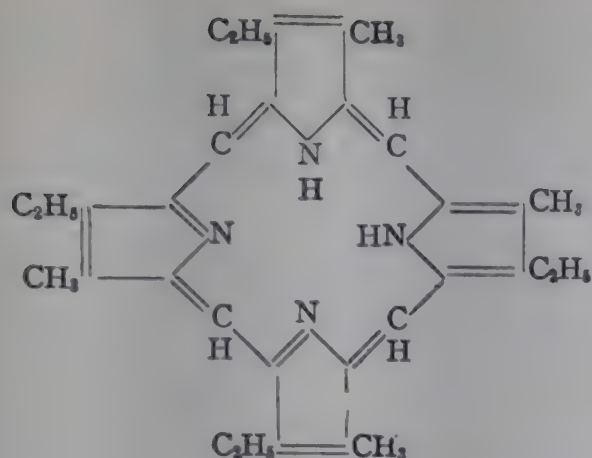


Aetioporphyrin ($\text{C}_{22}\text{H}_{30}\text{N}_4$)

This represents a porphyrin in its simplest state (*aetioporphyrin*) or rather the common nucleus of several porphyrins, for there are many different varieties. The distinctive characters of these latter are dependent upon atoms of carbon, hydrogen and oxygen attached as side chains to the basic nucleus.

Aetioporphyrin is the porphyrin of chlorophyll. *Protoporphyrin* is the porphyrin of the blood pigment. It has probably the following constitution (see p. 41), and is an isomer of *oophorphyrin*—the brown pigment of the egg-shell.

(*Metallo-porphyrins*. Porphyrins are capable of forming compounds with various metals.) A pigment found in the feathers of a certain South African bird (turaco), for instance, and known as



Protoporphyrin (C₃₂H₃₂N₄(COOH)₂)

turacin, is a porphyrin combined with copper; Laidlaw has synthesized a pigment almost identical with turacin by uniting a porphyrin with this metal. Other metalloporphyrins have been prepared, namely, those of cobalt, nickel, silver, manganese, tin, zinc, etc.¹ Protoporphyrin combined with iron forms the metallo-porphyrin of the blood pigment. For instance, if an Fe atom be attached to protoporphyrin we get the iron-porphyrin compound of hemoglobin. This is called *heme* (C₃₄H₃₂N₄O₄Fe). As we shall presently see, however, heme is not peculiar to hemoglobin but is a constituent of other respiratory substances.

Heme is capable of combining with various proteins or nitrogenous substances, e.g., albumin, ammonia, pyridine, nicotine, etc. Such compounds are called *hemochromogens*. When globin is the protein with which heme is combined the resulting hemochromogen is that forming the basis of the blood pigment of vertebrate life. Hemoglobin is, therefore, an iron + porphyrin + globin compound.

THE HEMOCHROMOGEN OF HEMOGLOBIN. When hemoglobin is treated with alkali, its characters are changed. Its spectrum differs from that of hemoglobin. It still is capable of combining with oxygen, but unlike hemoglobin it does not readily release the gas again. For many years this modified hemoglobin, to which the term *hemochromogen* was first applied, was thought to contain only the pigment fraction (porphyrin + iron) of the hemoglobin molecule; the globin supposedly had been "sheared" off. The work of Anson and Mirsky however, has shown that this assumption is incorrect. No separation of globin from the pigment fraction occurs. Hemochromogen is a porphyrin +

iron + globin compound, just as is hemoglobin. The globin, however, has been denatured by the action of the reagents and to this denaturation the properties of hemochromogen whereby it differs from hemoglobin are ascribed. The iron is in the ferrous state (Fe⁺⁺). Hemochromogen consists therefore of denatured globin combined with the pigment complex C₃₄H₃₂N₄O₄Fe (heme).

When hemochromogen is exposed to oxygen a true oxide is formed. This is called *cathemoglobin*. The heme is oxidized—*oxidized heme*—the iron being in the ferric state (Fe⁺⁺⁺). Cathemoglobin is therefore oxidized heme (C₃₄H₃₂N₄O₄FeOH) united to de-natured globin.² *Methemoglobin* is oxidized heme combined with native globin.

It is evident, therefore, that when the globin is in its natural state, oxygen is taken up loosely by heme (oxygenation) but when denaturation of the globin occurs the true oxide of heme (oxidation) is formed.)

HEMIN (C₃₄H₃₂N₄O₄FeCl) is the hydrochloride of heme and is prepared by heating oxyhemoglobin with glacial acetic acid and a minimal amount of sodium chloride. Upon cooling, reddish brown prismatic crystals of hemin separate out. The detection of these, which are frequently referred to as Teichmann's crystals after their discoverer, is used as a test for blood in suspected stains. When hemin is treated with caustic soda oxidized heme is obtained. When the latter is treated with a weak acid the iron is split off and protoporphyrin remains. Hemin or blood itself when treated with concentrated mineral acids in the presence of oxygen yields hematoporphyrin (p. 46).

THE DISTRIBUTION OF HEME IN NATURE

(Heme is almost universally distributed throughout the animal and vegetable kingdoms. Respiratory pigments with this porphyrin-iron compound as their common basis are found in the lowest forms of plant life as well as in the highest species of animals.)

(CYTOCHROME is a heme compound which is widely distributed in the tissues of plants and animals.) It is present in certain aerobic bacteria, in yeast cells, in the onion, in worms, molluscs, crustacea, in the muscles of the bee's wing and in many other insects and their larvae. It is present in the muscles and other tissues of the large number of vertebrate species which have

¹ In chlorophyll the porphyrin is combined with magnesium.

² Oxidized heme is called *hematin* by some and heme is referred to as *reduced heme* by Anson and Mirsky.

been examined, from amphibia to mammals. Cytochrome plays an important part in the oxidation system in the tissues (p. 328). It undergoes alternate oxidation and reduction but unlike hemoglobin is not autoxidizable or only slightly so (due to component *b*, see below). In order to take up oxygen it requires the aid of tissue oxidase (indophenol oxidase); in order to undergo reduction it requires the presence of dehydrogenases. These activate the hydrogen of organic molecules in the tissue cells which become hydrogen donors. The cytochrome acts as a hydrogen acceptor. In this way cytochrome, it is suggested, serves as an intermediary in the transference of oxygen, liberated from hemoglobin, to the oxidizable materials in the tissue cells. It may also through component *b* serve for the direct transference of oxygen. In the presence of cyanides, carbon monoxide (in the dark) or sulphides which poison the oxidase, the oxidation of cytochrome is inhibited. On the other hand, anesthetics which depress the action of dehydrogenases prevent its reduction. In either case the link in the chain of oxygen usage by the cells is broken.

Cytochrome is a mixture of three hemochromogens; they are referred to by Keilin as *a*, *b* and *c*. Of these only *b* is autoxidizable. The heme components of the hemochromogens are not all the same, there being two varieties. One of these is identical with that in hemoglobin, the other resembles that in chlorocruorin, see below. The nitrogenous compounds with which the hemes are combined are unknown. Cytochrome is identified in living tissues by its characteristic absorption spectrum. The cytochrome of bees' wing muscle shows four absorption bands at 6046, 5665, 5501 and 5270 Angstrom units [see p. 44], respectively. Its oxidation and reduction can be followed in the living cell by means of the microspectroscope, the bands becoming distinct when reduction occurs but almost disappearing when the substance is oxidized.

Heme in the free state, that is, uncombined with a nitrogen compound has been discovered in many substances such as wheat flour and oatmeal where it had never been suspected. The fact that heme is in one way or another of such universal occurrence has prompted Barratt to remark, "man kind has for countless centuries been eating, all unknowingly, the outstanding constituent of his blood." It has been frequently suggested in the past that chlorophyll which also is constituted of pyrrol rings, was the primitive pigment and that animals probably derived the pyrrol grouping for the manufacture of the pigment of their bloods from this green coloring

matter in their diet. It is now seen, however, that heme is a much more ancient pigment; it is found in the most elemental forms of life in which chlorophyll does not exist. It is pointed out, however, on page 57 that the little evidence that either of these pigments in the diet serves as a basis for hemoglobin synthesis.

Hemoglobin itself is by no means so widely distributed as is heme and the heme component, cytochrome, for it is confined to the animal kingdom. It is found in the blood of all vertebrates and of several invertebrates, e.g., worm, certain snail, in the larvae of some but not in the body fluids of any adult insect. The blood components of different vertebrate species vary in their properties, the hemoglobin of the frog, for instance, possesses a different spectrum and oxygen dissociation curve from that of mammals. This variability is due to minor differences in globins to which the heme is joined and not to different hemes, which are the same throughout the vertebrate phylum.

Though many different porphyrins exist, only differing from protoporphyrin has been discovered in nature as forming part of a hemoglobin-like substance, i.e., one in which the nitrogenous fraction is probably a globin. A hemoglobin-like pigment, greenish color, is found in certain worms and is called *chlorocruorin*. It contains this other porphyrin of unknown structure combined with iron. *Helicorubin* is a respiratory pigment found in the gut and liver of snail. It contains the same heme as hemoglobin, as shown by the fact that if its non-pigmented fraction be replaced by pyridine the pyridine-hemochromogen so formed shows a spectrum identical with that of pyridine-hemochromogen derived from hemoglobin. *Chlorocruorin*, however, since its heme is different when treated similarly shows a different spectrum. The nitrogenous part of *helicorubin* is unknown, presumably it is not globin.

Hemerythrin is a respiratory pigment which occurs in certain crustacea and molluscs (king crab, octopus, snail) takes the place of hemoglobin. It is dissolved in the circulating fluid and not confined within cells. This substance contains copper instead of iron; the metal is not combined with a porphyrin as is believed at one time. This pigment is blue when oxidized and colorless when reduced.

SUMMARY

Some of the points in the preceding paragraphs may be summed up in the following scheme:

(Pyrrol nucleus)₄ = a porphyrin compound
 Porphyrins + metals = metallo-porphyrins, hemes

Protoporphyrin + iron (Fe^{++}) = heme

Heme + various nitrogenous substances = hemochromogens of various respiratory pigments, e.g., cytochrome, helioerythrin, etc.

Heme (iron in ferrous state) + globin = hemoglobin (see also scheme on p. 45)

Heme + denatured globin = hemochromogen of hemoglobin

Oxidized heme (iron in ferric state) + denatured globin = cathemoglobin

Oxidized heme + globin = methemoglobin (p. 44)

THE MOLECULAR WEIGHT OF HEMOGLOBIN

The pigment proper (heme) constitutes about per cent and the globin about 96 per cent of the hemoglobin molecule. The small but relatively heavy porphyrin-iron portion is floated, as it were, by the large protein fraction. If hemoglobin contained only 1 atom of iron which has a molecular weight of 56, then since the percentage of the metal in hemoglobin is 0.336, as determined by direct analyses, the minimum molecular weight of hemoglobin would be $\frac{56}{0.336} \times 100 = 16,700$, approximately. Hufner obtained in fact a figure of 16,800 from osmotic pressure measurements.

Adair, however, from a study of the osmotic pressure of hemoglobin finds the molecular weight to be approximately four times greater, namely, 68,000. The molecule contains 4 atoms of iron. Using an entirely different but most ingenious physical method, namely, ultracentrifugation, Svedberg obtained a value almost identical with Adair's. Solutions of hemoglobin were centrifuged at great speeds for several hours so as to force the sedimentation of the hemoglobin molecule, which under ordinary circumstances of course, does not separate from solution. When a solution is subjected to a centrifugal force 200,000 times that of gravity, a conflict between two opposing forces occurs. Centrifugal force tends to throw the particles down out of the solution, diffusion, on the other hand, tends to prevent their sedimentation. The rate of sedimentation will therefore be a measure of the degree to which the centrifugal force overbalances the rate of diffusion. The rate of diffusion but not that of sedimentation depends upon the molecular weight. So it is possible to calculate the molecular weight indirectly from an equation based upon the sedimentation value but also including a number of other factors.

Northrop and Anson also obtained a figure of around 68,000 from calculations based upon the rate of diffusion of hemoglobin through discs of alundum. Hemochromogen is probably a depolymerized form of hemoglobin with a molecular weight of 16,700, or double this value.

Human blood contains about 15 grams (14 to 16 grams) of hemoglobin per 100 cc. Since the proportion of iron in hemoglobin is 0.336 per cent, the quantity of the metal in 100 cc. of blood is about 50 mg. and in the total blood of the human body about 4 grams. The total quantity of hemoglobin of an average sized man is about 1 kg. or about 14 grams per kilogram of body weight. The blood contains a small proportion of iron in addition to that combined with hemoglobin (p. 58).

THE ESTIMATION OF HEMOGLOBIN IN BLOOD. A determination of its oxygen capacity is the most accurate means of obtaining the hemoglobin concentration of a sample of blood (p. 318). A number of clinical methods are available for estimating the hemoglobin concentration as a percentage of the normal. Only one, namely that of Gowers as modified by Sahli and by Haskins, will be described. Dilute HCl (0.2 N) is placed in a small graduated glass tube up to the mark 10. 0.02 cc. of the blood under examination is delivered into the acid with a Sahli pipette which is rinsed by drawing the acid blood mixture into it twice and blowing out each time. The tube is kept at a temperature of about 60°C. for 7 minutes. When the full reddish brown color of the acid hematin (hemin) which is formed has fully developed, the tube is placed in a comparator alongside a standard color solution and carefully diluted with water until the two colors exactly match. The hemoglobin percentage is given by the figure on the tube at the level of the mixture. The temperature of the standard should be kept at around 20°C. while the color comparison is being made. Blood containing 13 grams of hemoglobin per 100 cc. gives a reading of 100 per cent. The blood of the average healthy person would therefore give a reading of 110 per cent.

Myoglobin or muscle hemoglobin, the pigment of muscle, resembles blood hemoglobin in its function. It acts as an oxygen reservoir within the muscle fiber which serves to tide the muscle over from one contraction to the next. It has a higher oxygen affinity than has blood hemoglobin and can combine with oxygen and dissociate from it with great rapidity (less than 1/100 second). Myoglobin starts to give up its oxygen at the instant that the muscle contracts. Its oxygen store is replenished during the resting state.

COMBINATIONS OF HEMOGLOBIN WITH GASES

Oxygen (see also chapter XXXII)

Hemoglobin combines with oxygen by virtue of the iron which it contains. The two elements combine according to the law of definite propor-

tions, two atoms of oxygen uniting with each atom of iron in the hemoglobin complex. Thus



The combination of oxygen with hemoglobin is a most unstable one. When the oxygen pressure of the atmosphere in contact with hemoglobin is raised, oxygen is taken up but no true oxide is formed. The iron remains in the ferrous state. It is the globin which endows the iron-pigment part of hemoglobin with the unique property of forming a loose combination with oxygen: the latter is lost once denaturation of the protein occurs. Hemoglobin *oxygenated* (not *oxidized*) in this way is known as *oxyhemoglobin*. The term *reduced hemoglobin* implies that the pigment has given up a part of its oxygen store.

The capacity of the blood for absorbing oxygen—the *oxygen capacity* as it is called is proportional to the hemoglobin concentration. The oxygen capacity of a gram of hemoglobin is 1.34cc. So the oxygen capacity of 100 cc. of normal human blood (15 grams Hb) is ($15 \times 1.34 =$) 20 cc. The union of oxygen with hemoglobin will be dealt with more fully in the section on respiration.

METHEMOGLOBIN. This is a true oxide. One atom of oxygen combines with one of iron, and the gas cannot be removed by exposing the blood to a vacuum; it can be removed only by chemical reagents. Methoglobin is, therefore, a compound of oxidized heme (i.e., heme containing ferric iron) with native globin and thus differs chemically from cathemoglobin which is ferric heme plus de-natured globin. When potassium ferricyanide is added to oxyhemoglobin, as in the Haldane method of determining the oxygen content of a sample of blood (p. 318), the two loosely bound atoms of oxygen are easily displaced but the iron is oxidized by the reagent and methemoglobin formed.¹ In poisoning by certain drugs, e.g., nitrites, chlorates, sulphates, acetanilid, bismuth subnitrate, nitrobenzine compounds, sulphanilamide, etc., the blood becomes dark in color due to the formation of methemoglobin and gives rise to a type of cyanosis (p. 373) to which the

¹ The change is explained in the following way. The ferricyanide oxidizes the reduced hemoglobin which is in equilibrium with the oxyhemoglobin



The equilibrium is re-established by the passage of oxyhemoglobin into the reduced state, i.e., the oxyhemoglobin gives up its oxygen with the result that a loose compound of oxygen with hemoglobin is replaced by a true oxide of hemoglobin, i.e., methemoglobin

term "toxic" is applied.⁴ The discoloration of the skin becomes evident when the methemoglobin amounts to about 3 grams per 100 cc. of blood. Methylene blue when injected into the blood stream causes the formation of methemoglobin. The employment of this dye in the treatment of cyanide poisoning is dealt with on page 373.

Sulphemoglobin

Reduced hemoglobin combines with hydrogen sulphide to form sulphemoglobin which gives blood a chocolate color. Except perhaps extreme cases of intestinal putrefaction hydrogen sulphide is not absorbed in appreciable amount. But it appears that certain drugs notably acetanilid

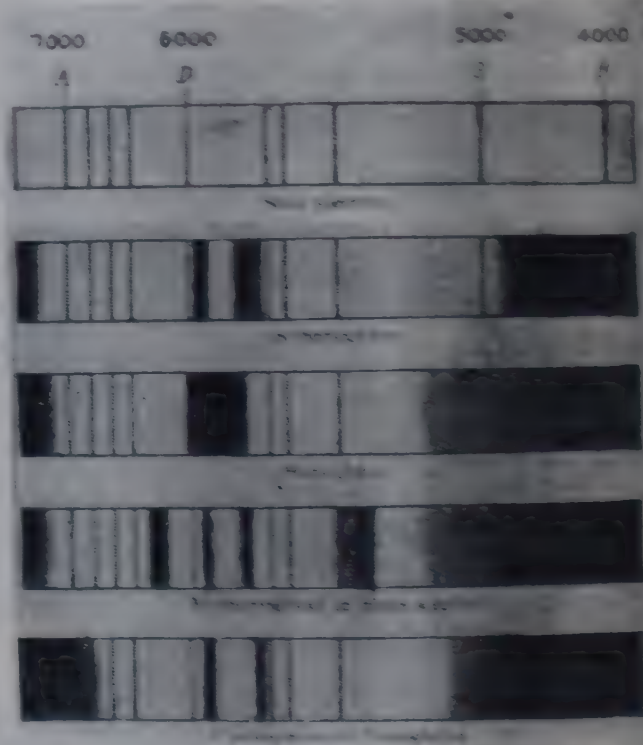
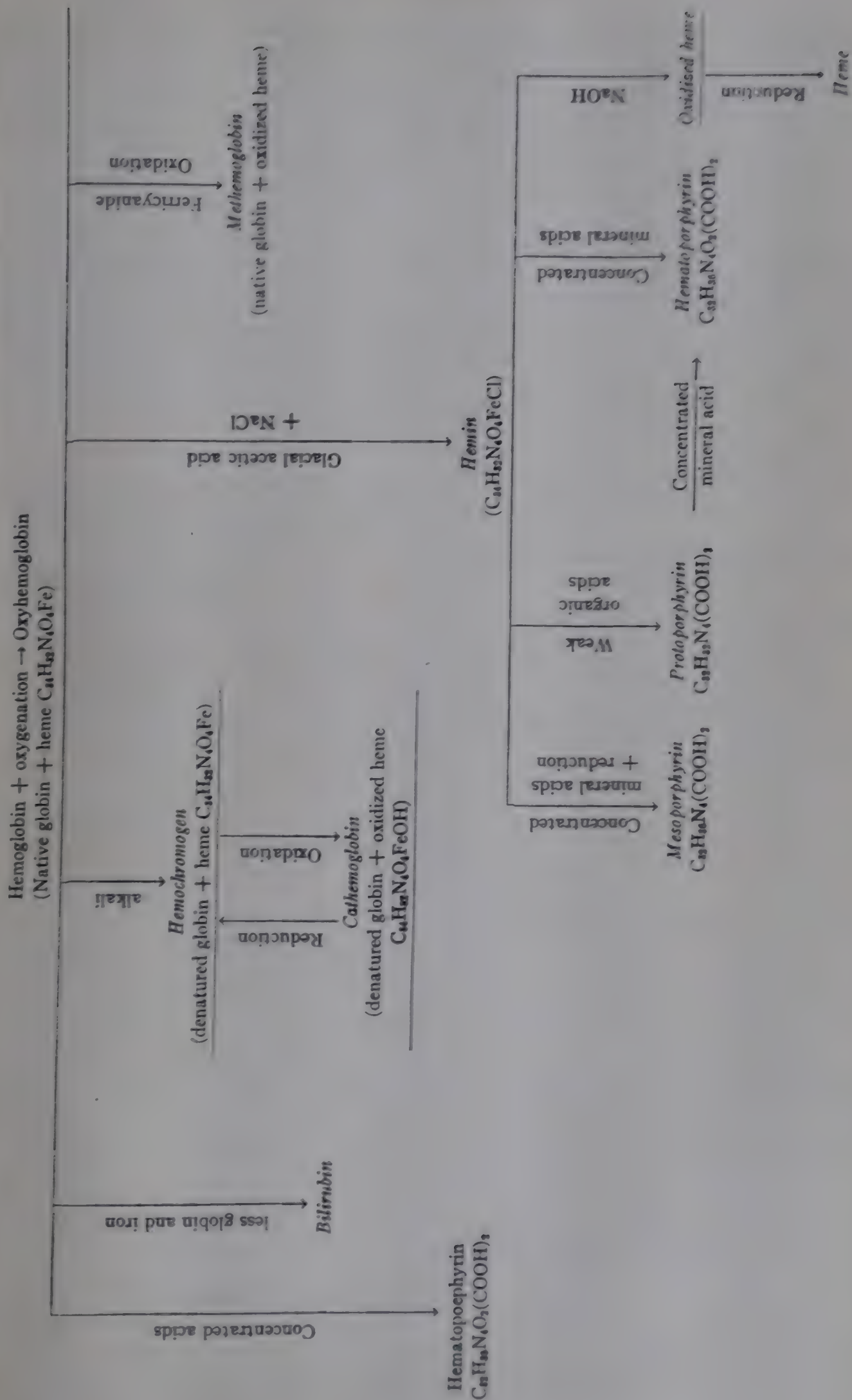


FIG. 14. Absorption spectra of hemoglobin and some of its derivatives (after Peterson, Haines and Webster, *Legal Medicine and Toxicology*).

(which is contained in bromo-seltzer) and phenacetin sensitize hemoglobin so that it combines more readily with hydrogen sulphide. Small quantities of the gas absorbed from the alimentary canal may then cause sulphemoglobin to reach a relatively high concentration in the circulation and give a bluish or mauve tint to the skin. This so-called *enterogenous cyanosis* occurs when an abnormal compound amounts to from 3 to 5 grams per 100 cc. of blood. The presence in the blood of sulphemoglobin or of methemoglobin is detected by spectroscopic examination (fig. 14).

⁴ According to Meulengracht and his associates the cyanosis caused by acetanilid is due to the decomposition of the drug to dark colored derivative para-amido-phenol rather than to the formation of methemoglobin.



Carbonyl-hemoglobin and nitric oxide hemoglobin

Carbon monoxide combines with hemoglobin in the same proportion as does oxygen. It competes successfully with the latter for hemoglobin and displaces it volume for volume to form carboxyhemoglobin. Unlike oxygen, however, it forms with hemoglobin a stable compound which can be disrupted only with the greatest difficulty. The much greater avidity (between 200 and 250 times) which hemoglobin shows for CO renders the gas so highly dangerous when inhaled in any considerable quantity (see p. 371). **Nitric oxide** gas also has a strong affinity for hemoglobin and forms a stable compound with it. The fumes given off by high explosives during their combustion contain large amounts of nitric oxide and the commonest way in which this poisoning occurs is through persons entering a closed space after an explosion, before the gas has cleared away.

Pigment complexes derived from hemoglobin but free from iron and globin

Hematoporphyrin, $C_{54}H_{54}O_8N_4(COOH)_8$, is an artificial derivative obtained by the action of strong mineral acids upon hemoglobin or upon hemein. It is closely related to protoporphyrin—the natural porphyrin of hemoglobin but contains two more molecules of water. By reduction hematoporphyrin is converted to **mesoporphyrin** $C_{54}H_{54}N_4(COOH)_8$.

Coproporphyrin, $C_{52}H_{52}N_4(COOH)_8$, formed in the intestine from bilirubin is found normally in human feces, and in urine, bile and milk in traces.

Uroporphyrin, $C_{54}H_{54}N_4(COOH)_8$, is present in minute amounts in normal urine. The copper salt of this porphyrin is **turacin** mentioned on page 41. Coproporphyrin and uroporphyrin are produced in excessive quantities in the condition known as **hematoporphyrin**. Neither of them, however, is derived in the body from the breakdown of hemoglobin. Under normal circumstances they are largely derived from the porphyrins of plant and animal tissues taken as food. Their excretion is therefore moderately increased by a diet of high porphyrin content, e.g., meat and certain vegetables. Hematoporphyrin and uroporphyrin when injected into animals causes them to become highly sensitive to the rays of visible light. If given a large injection and then placed in a bright light, urgent symptoms quickly appear and death results. If the animal is kept in the dark no ill effects result. If smaller doses of the porphyrin are given over a period erythema, eczema and other skin lesions develop.

Bilirubin, $C_{43}H_{56}N_4O_6$ (p. 433) contains the four pyrral groups but the arrangement of these has been changed so that they no longer form the ring structure typical of a porphyrin. By oxidation of bilirubin in

its passage through the liver biliverdin, $C_{43}H_{56}N_4O_6$, is formed. Bilirubin is converted by reduction in the intestine to stercobilinogen, also called urobilinogen (p. 410). Urobilin, is formed by the oxidation of stercobilinogen, and is present in very small quantities in normal urine, but is not the pigment responsible for the color of urine (p. 398).

Absorption spectra. The various heme pigments and the compounds of hemoglobin when placed in the path of a beam of white light absorb waves of certain lengths but transmit the rest. That is, each possesses a characteristic absorption spectrum and it is by means of spectroscopy that they may be most readily detected. The different hemochromogens, reduced hemoglobin and oxyhemoglobin, CO and NO hemoglobin, hematoporphyrin, coproporphyrin, cytochrome, urobilin, etc. have all their specific absorption bands. See table 8.

TABLE 8

Wave lengths (λ) at the points of maximum intensity of absorption bands of hemoglobin and its derivatives as well as some of the other heme compounds

COMPOUND	NUMBER OF BANDS	SITUATIONS OF ABSORPTION BANDS WAVE LENGTHS IN ANGSTROM UNITS			
Oxyhemoglobin	2	5760	5448	—	—
Reduced hemoglobin	1	5650	—	—	—
Carboxyhemoglobin	2	5709	5350	—	—
Methemoglobin	4	6300	5780	5400	5000
Sulphemoglobin	3	6180	5780	5400	—
Hemochromogen	2	5585	5275	—	—
	2	5580	5270	—	—
Reduced heme	2	6070	5820	—	—
Cytochrome	4	6046	5665	5300	5210
Protoporphyrin (in acid)	2	6000	5540	—	—
Urobilin	1	4900	—	—	—

Hematoporphyrin. This is a condition due to disordered porphyrin metabolism. Large quantities of uroporphyrin and coproporphyrin are excreted, the former giving a port wine color to the urine. The bones and teeth may be stained brown or pink by the pigment. It is unfortunate that the disease has been called hematoporphyrin for as just mentioned the porphyrins produced in excess are uroporphyrin and coproporphyrin and not hematoporphyrin which is an artificial substance resulting from the action of laboratory reagents. The condition is frequently congenital and runs a chronic course but it may be acute and arise from no known cause or may follow the prolonged use of such drugs as sulfonal or trional and possibly veronal. The disease has a high mortality. During life, symptoms referable to the gastrointestinal tract and nervous system, e.g., abdominal pain, nausea, vomiting and an ascending paralysis, are prominent. In the chronic cases sensitivity to light rays is evidenced by skin eruptions, e.g., erythema, vesic-

bullae, and the port wine color of the urine are the features. In hematoporphyria the porphyrins are not believed to be derived from the breakdown of hemoglobin. Coproporphyrin or uroporphyrin can be obtained from hemoglobin by laboratory means, without disrupting the pyrrol grouping and it is unlikely that the body can effect the transformation. There is, as a rule, no evidence of any abnormal destruction of red cells and in animals destruction of red cells induced by various means does not increase the output of porphyrins. It is thought rather that the disease is due to overproduction of these porphyrins at a certain stage in hemoglobin synthesis—a reversion to an embryonic type of pigment metabolism. The red cells of the embryo contain uroporphyrin as well as hemoglobin. Porphyrin is also present in the primitive

cells found in certain anemias. Hemoglobin is a more highly specialized type of the more generally distributed and more primitive respiratory pigments. It is not improbable that such heme pigments serve purposes in the early embryonic life of mammals which are served in later embryonic life and in the adult by the more highly specialized hemoglobin. At a certain stage in development hemoglobin production from these pigments would commence. Primitive pigments and hemoglobin would thus be formed at the same time. In hematoporphyria it is suggested that the primitive type of pigment formation persists.

Though there is no evidence, it is possible that the porphyrins in this disease are derived from myoglobin, cytochrome or other porphyrin compounds of the tissues.

CHAPTER VII

HEMOLYSIS AND SUSPENSION STABILITY OF THE BLOOD

HEMOLYSIS OR THE LAKING OF BLOOD

Under normal circumstances the plasma contains no appreciable quantity of hemoglobin. If normal blood be centrifuged the corpuscles are driven to the bottom of the tube while the supernatant plasma is clear but faintly straw-colored. Under certain conditions, however, changes may occur in the red cell which will allow the hemoglobin to escape into the surrounding fluid, which then becomes discolored. This² is called *hemolysis* or *laking*, and may be carried out in a test tube by means of various agencies both physical and chemical. Certain biological substances, such as the toxins of bacteria, snake venoms, are intensely hemolytic. On the other hand, substances belonging to the class of immune substances or antibodies, and known specifically as hemolysins, are formed in the blood. These have the power to hemolyse foreign red cells. After the action of certain hemolytic agents the dim colorless outline of the red cells—shadow cells or “ghosts”—may be seen; they represent the incompletely destroyed framework of stroma.¹ (See frontispiece.) Some of the means by which hemolysis may be induced may now be considered in greater detail.

(1) Hypotonic solutions

The membranes of plant and animal cells are semipermeable (p. 23). They allow the passage into the cell of water and various substances in solution, but offer a barrier to the entrance or egress of others. The red cell is no exception; it contains substances (p. 339) which cannot pass out, and is surrounded by a fluid (plasma) containing materials which cannot pass in. We have here then a minute and almost perfect osmometer (p. 23), and indeed much of our knowledge of osmotic phenomena has been gained from the study of the behavior of plant and animal cells when placed in solutions of different concentrations. In normal blood the plasma and the corpuscles are in osmotic equilibrium, i.e., the fluids separated by

the corpuscular membrane are isotonic. If, however, the dissolved substances in the plasma be diluted by the addition of distilled water, a flow of water into the corpuscles occurs. An osmotic pressure is developed within it which the cell membrane is unable to withstand. The cell swells and becomes globular, the membrane stretches and finally bursts, liberating its hemoglobin.

The process is in reality rather more complicated than this. It is probable that the hemoglobin is not contained within the red cell merely as in a bladder, or even in a number of smaller compartments, but is bound in some way to the cell structure.³ One reason for this belief is that purely mechanical agencies will not liberate the pigment. The cell may be torn into the finest shreds, yet each minute particle still retains its hold upon the hemoglobin. The pigment, however, is soon released when the surrounding fluid is made hypotonic. This suggests that the cell structure consists of semipermeable partitions of almost infinite fineness.

The normal red cell offers a certain resistance to the disintegrating effect of hypotonic solutions. A slight lowering of the osmotic pressure of the surrounding fluid will not produce hemolysis. The normal percentage of salts in human plasma is approximately 0.94. Normal cells may be placed in a 0.6 per cent saline solution without being hemolyzed. The cell increases in volume, but the membrane remains intact. Hemolysis commences when the saline concentration is reduced to about 0.40 per cent and is complete at 0.34 per cent. The resistance which erythrocytes offer to the hemolytic action of hypotonic solutions is used in this way as an index of the fragility of the red cells. In pernicious anemia the red cells have been found to be actually less fragile than normal whereas in other conditions, e.g., some forms of purpura (p. 94) and chronic hemolytic jaundice, their fragility is increased.

The permeability of the membrane of the red cell is therefore quite different from that of the capillary membrane which as we have seen (p. 42) allows the passage of all crystalloid substances and

¹ When hemolysis is induced by certain reagents, e.g., linoleic acid, but the cell structure remains intact, the addition of electrolytes causes the reappearance of hemoglobin in the cells (“reversed hemolysis”). This phenomenon is due probably to shrinkage of the cells and the concentration of unliberated pigment and not to the return of hemoglobin to the cell.

³ According to Schafer the red cell is simply a drop of colored fluid enclosed by a membrane, but it is difficult to explain the very definite shape of the cell without presuming that it possesses a stroma of some sort.

to some extent of plasma protein; it is also freely permeable to hemoglobin. The membrane of the erythrocyte, on the other hand, is impermeable to hemoglobin and the plasma proteins and to the cations Ca^{++} , K^{+} , Mg^{+} and H^{+} , but permits the passage of water and the anions Cl^{-} , HCO_3^{-} , OH^{-} and PO_4^{-} . It appears that, contrary to previous belief, the erythrocyte is permeable to sodium. Since the cell is impermeable to the smaller K ion, its selective permeability cannot be explained simply upon the theory that the cell membrane is a sieve-like structure whose "pores" are of such a size as to allow the smaller ions, but not the larger ones, to pass. The lipid-soluble theory is also unsatisfactory, for the inorganic anions are lipid-insoluble. The cell membrane is freely permeable to amino acids, urea and uric acid, so these substances under ordinary circumstances do not enter into the osmotic relationships between cells and plasma. Osmotic changes occur, however, when CO_2 enters the blood and diffuses into the cell (see p. 337).

(2) Chemical substances

Ether, chloroform benzene and alcohol act by dissolving the lipid constituents of the envelope and stroma of the cell. Other substances, e.g. *bile salts, acids and alkalis* and *saponin* cause hemolysis, but the manner in which they act is not altogether clear. Bile salts probably act by combining with the protein constituents, and saponin with the cholesterol. As a result of the chemical changes induced by either of these substances, destruction of the cell stroma—*stromatolysis*—occurs. Acids probably act by penetrating the cell and increasing the osmotic concentration within. Swelling and liberation of the hemoglobin occurs in a manner analogous to that of hypotonic solutions. The stroma is not as a rule destroyed. Alkalis, particularly ammonia, are powerfully hemolytic, as is also ammonium chloride. The NH_3 enters the cell and through the increase in osmotic pressure causes swelling and liberation of the hemoglobin. Stromatolysis occurs following the hemolysis by alkali.

Certain chemical poisons such as carbolic acid, nitrobenzene, pyrogallol, ricin, arsenical preparations used in the treatment of syphilis, and many other substances are capable of causing red cell destruction.

(3) Substances of bacterial origin or formed in the animal body

(a) SPECIFIC HEMOLYSINS. If blood be injected into the veins of an animal of another species, or as already mentioned (p. 35) into an individual of the same species but whose blood group is incompatible with the blood group to which the injected blood belongs, agglutination of the red cells of the donor occurs, and hemolysis fol-

lows as a secondary effect. But if a series of injections of erythrocytes be injected over a period of days into the blood of another species the serum of the latter develops a substance which promptly destroys the foreign cells through a *primary* hemolytic effect quite independent of agglutination. This hemolytic reaction, which was first demonstrated by Bordet, is specific, that is to say, it is only the particular species of erythrocyte to which the animal has been sensitized by previous injections that is destroyed by the hemolytic substance. The latter on this account is known as a *specific hemolysin*. It belongs to the class of immune substances or antibodies. Bodies of similar nature cause the destruction of other foreign cells and are known as cytolytins and bacteriolysins. All are part of a general protective mechanism which the body is able to build up against the invasion of foreign cells. When referring to these and other immune reactions the substance which upon entering the body causes their development is referred to as the *antigen* (i.e., the foreign red cells in the case of hemolysins). The antibody itself (e.g., the hemolysin) is heat stable and is spoken of as the *amboceptor*. The latter which is specific requires for its action another body which is nonspecific, is present in all sera and is destroyed by heat. It is known as the *complement*. Three factors (antigen, amboceptor and complement) are therefore necessary for the hemolytic or bacteriolytic reaction. After the action of the hemolytic or bacteriolytic amboceptor has been annulled through destruction of the complement by heat, the reaction may be restored by the addition of any serum (i.e., by supplying fresh complement).

When serum which has developed a bacterial antibody is incubated with an emulsion of the particular bacteria which has served as antigen, a reaction occurs which "fixes" or binds the complement. The phenomenon is spoken of as *complement fixation*. These facts were applied by Wassermann to the diagnosis of syphilis, and by subsequent workers as a test for other diseases, e.g., tuberculosis. For example, the previously heated serum of a subject suspected to be suffering from syphilitis, is incubated with (a) an emulsion of syphilitic liver¹ tubercle or typhoid bacilli respectively (the antigen) together with (b) complement furnished by normal guinea-pig's serum. If the suspected serum contains a specific antibody (amboceptor) for the antigen employed, the former will bind the complement to the latter, i.e., fixation of complement will occur. The foregoing is an account of a bacteriolytic system. An hemolytic system is employed to render the reaction visible. Washed sheep's corpuscles are added to the former system, together with the previously heated serum of a rabbit which has been sensitized to the latter cells by repeated injections. This serum supplies the hemolytic amboceptor but its complement has been

¹ As a matter of fact syphilitic liver has been found to be unnecessary, since lecithin and other materials for some unexplained reason will serve as antigens.

destroyed. If the test is positive no hemolysis of the corpuscles occurs, since the complement (non-specific) of the patient's serum has been already fixed by the bacteriolytic amboceptor and the hemolysin of the rabbit serum is therefore unable to exert its usual effect.

(b) **TOXIC SUBSTANCES OF BACTERIAL OR PARASITIC ORIGIN.** *Endogenous* poisons of unknown origin. The toxins of bacteria responsible for many diseases, e.g. streptococcus, staphylococcus, tetanus bacillus and the organism of scarlet fever or the malarial parasite may cause a destruction of red cells. The more virulent types of other infectious fevers, e.g., smallpox, diphtheria, are also sometimes accompanied by intense hemolysis. When the hemolysis is of moderate degree but occurs over longer periods the hemoglobin is converted into bile-pigment. This, if formed in amounts greater than can be disposed of by the liver, undergoes partial retention in the plasma, which together with the solid tissues, especially of the skin and mucous membranes, becomes stained a yellowish tint—hemolytic jaundice (p. 463). In hemolytic states of long standing an iron containing derivative of hemoglobin termed *hemosiderin* is frequently deposited in large amounts in the tissues, particularly of the liver and spleen (p. 60).

When the hemolysis reaches such a degree that the hemoglobin cannot be converted into bilirubin as rapidly as it is liberated, as in severe malaria (black-water fever) *hemoglobinuria* occurs, that is, the pigment is passed in the urine, which is usually turned a dark brown or even black color, due to the action of the urinary acid in converting the pigment into methemoglobin. The concentration of hemoglobin must, as a rule, reach a level of about 0.7 gram per 100 cc. of blood before it appears in the urine. It should be remembered that hemoglobin once it has escaped from the erythrocytes is functionless. Not only is it unable to be retained within the capillaries on account of the relatively small size of its molecule but the environment of the plasma is unsuitable for its action. An endogenous poison of some sort is probably responsible for the hemolysis that occurs in the condition known as *paroxysmal hemoglobinuria*. An attack of this disease is precipitated most usually by chilling of the body surface, but may follow emotional disturbances or undue muscular exertion. The condition is sometimes associated with Raynaud's disease, in which condition spasmodic constrictions of the small vessels of the peripheral parts of the body occur, particularly after exposure to cold. The occasional association of the two conditions has suggested to some that they have a common cause. Direct evidence for this, however, is wanting. It is an interesting and suggestive observation that though the cells of normal blood are unaffected by cold, the blood of a subject of paroxysmal hemoglobinuria if cooled (to 5°C.) outside the body and subsequently warmed undergoes hemolysis (Donath phenomenon). There is apparently no defect, however, of the subject's corpuscles; they seem to be no less resistant than normal to hypotonic saline; the serum,

on the other hand, has the power to hemolyze the cells of a normal person. The great majority of subjects give a positive Wassermann reaction.

March hemoglobinuria. Hemolysis may occur and hemoglobin appear in the urine even in healthy persons after strenuous muscular effort. In certain persons this tendency is exaggerated and hemoglobinuria may follow relatively mild muscular exercise. It is seen not infrequently in soldiers after long marches. The free pigment in the blood and urine of such cases is erythromyoglobin, not myoglobin as might be expected. The fragility of the red cells is not increased and no hemolysins nor autoagglutinins which might account for the hemolysis have been discovered.

In a third type of paroxysmal hemoglobinuria—the *nocturnal hemoglobinuria of Marchiafava*—hemoglobin or hemosiderin (p. 60) is passed almost continuously in the urine, but in greatest amounts at night. It is accompanied by a severe hemolytic anemia.

(c) *The Venoms of Certain Poisonous Snakes*, e.g. the cobra, and the poisons of various stinging insects and spiders cause a destruction to a greater or less degree of the red cells. Snake venom (cobra) has been shown to act indirectly. It contains a principle which has power to remove unsaturated fatty acids from the lecithin molecule. The resulting product which is called *lysolecithin*, is intensely hemolytic. Since lecithin is present both in erythrocytes and plasma and indeed in all cells, the entrance of snake venom into the body causes the production of this intensely hemolytic substance. Cephalin is acted upon by snake venom in a similar manner with the production of *lysocephalin* which has a similar hemolytic action.

THE SUSPENSION STABILITY OF THE BLOOD

The blood is a suspension of cells in a viscous fluid, the plasma. It is only the constant movement of the fluid that keeps the cells evenly distributed throughout. When the circulation comes to rest the cells at once commence to sink. Under ordinary circumstances the sedimentation of the cells, even in the blood withdrawn from the body, can progress to only a negligible extent, for it is soon circumvented by the clotting process which fixes them in a jelly-like matrix. If for any reason the blood is delayed from clotting, sedimentation may continue until an upper layer of clear plasma becomes separated from the cells which have descended through the fluid. When clotting then ensues the blood consists of two strata, a thin yellowish or buff-colored layer of clotted plasma laid upon a much deeper red stratum of cells. When blood had clotted in this way the upper layer was known to the older physiologists as the "buffy coat" (see also p. 88), while the ancient

thought it was the "phlegm" of the blood which had undergone separation from the other humors.

It has been shown by Fahraeus that the rate of sinking—the *sedimentation rate*—of the red cells varies in disease and under certain conditions of health. The rate is measured by the depth in millimeters of clear plasma which is formed at the top of a vertical column of blood by the end of one hour. The blood for examination is diluted 4 parts to 1 of a 3 per cent solution of sodium citrate. It is then drawn into a glass tube, with a bore of 2.5 mm. to a height of 60 mm.⁴ The upper end of the tube which is fixed in a strictly perpendicular position is left open, while the lower end is closed by a rubber cap held in position by a spring. The sedimentation rates of clear plasma

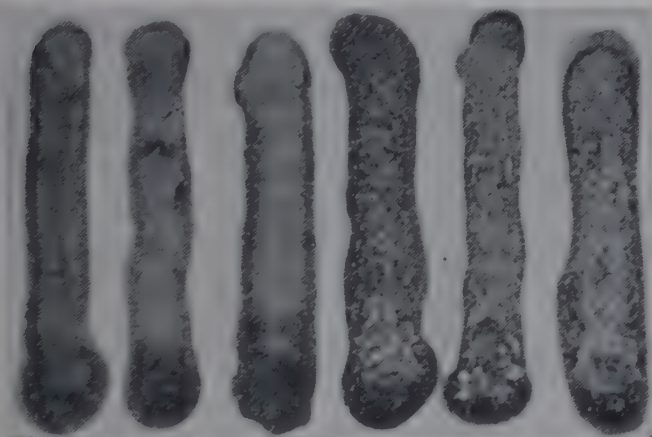


FIG. 15. Showing the naked-eye appearances of specimens of blood spread upon glass slides. The specimens, left to right, are from, *a.* healthy man (2), *b.* healthy woman (7), *c.* healthy pregnant woman (28), *d.* man, appendicitis (40), *e.* man, pneumonia (68), *f.* sepsis (102). Note granular appearance of specimens *d.*, *e.*, and *f.* Figures in brackets indicate sedimentation rates, mm. per hour (after Fahraeus).

per hour were found for different normal bloods to be as follows:

	mm. per hour
Men.....	1-3
Women.....	4-7
Newborn children.....	0.5

These figures for the sedimentation rate are an index of what is termed the suspension stability of the blood. In normal pregnancy and in certain pathological states, the sinking rate of the red cells is found to be very markedly increased; in other

⁴In some methods the blood is drawn to a higher level than this, but according to Walton the most consistent results are obtained with a column of blood of this height. Since the concentration of the blood in red cells influences the sinking rate, it is also recommended that their number be standardized to 5,000,000 cu. mm. by the addition or removal of plasma if the subject's blood is below or above this level.

words, the suspension stability of the blood is reduced. The average figure during pregnancy is about 35 mm. per hour. The rate is also increased during menstruation. The pathological states which show the most noteworthy increase in the rate are septicemia, 100 mm. per hour, and pulmonary tuberculosis, 65 mm. Anemia, malignant tumors, inflammatory conditions of the female pelvic organs and many other conditions moderately increase the rate above the normal. *Reduction* in the sedimentation rate is rare; it occurs in allergic states, in peptone shock and in sickle-cell and hemolytic anemias.

The physical changes in the blood which might cause this unusually rapid rate of red cell settling are of considerable interest and were investigated thoroughly by Fahraeus. In considering the sedimentation rate of particles suspended in a fluid when they are of a size comparable with that of the red cells, four factors must be taken into account. These as applied to blood are:

(1) *Specific gravity* of the plasma as compared with that of the corpuscles. Corpuscles of high specific gravity would sink more quickly in normal plasma, and normal corpuscles would settle more quickly in a plasma with a low specific gravity. In neither corpuscles nor plasma was any significant change of this nature discovered.

(2) *Lowered viscosity* of the plasma is another factor which could cause an increase in rate of sinking, but no such change could be detected.

(3) *Increased size of the corpuscles* would increase their mass disproportionately to their surface and in consequence enhance their rate of sinking, but no significant alteration in size was found.

(4) *Clumping* together of cells of normal size would have the same effect as an increase in size of the individual cells for just as lumps of clay sink rapidly in water, while clay in the form of fine particles remain suspended almost indefinitely, so aggregation of the corpuscles would cause their more rapid sedimentation.

This last factor was found to be the cause of the lowered stability of the blood suspension in the pathological conditions cited above. The roughness and granular appearance of the blood, due to the corpuscular aggregation is evident to the naked eye when the blood is spread in a film upon a slide (fig. 15). Normal blood, in marked contrast, forms a smooth homogeneous film. Under the microscope the crowding together of the cells in large masses is quite obvious. An increase in the fibrinogen and globulin fractions of the plasma is held responsible for the effect. These proteins act upon the corpuscles in some unknown way to make



them adhere to one another and form clumps of agglutinated cells⁶ (auto-agglutination). That the character of the plasma and not that of the cells is the determining factor is shown by the fact that if erythrocytes from blood with a high sedimentation rate (e.g., of pregnancy) are suspended in the plasma of blood having a low rate of sedimentation (e.g., of newborn) they settle at the slower rate.

⁶ The red cells of normal blood show an incipient tendency to cling together in chains—the so-called *rouleaux* formation.

The non-specificity of the test is evident; nevertheless determinations of the sedimentation rate are of considerable value (1) in gauging the degree of activity of tuberculous processes; (2) as an aid in the differential diagnosis of certain gynecological lesions. Benign tumors of the pelvic organs cause no change in rate whereas, as already mentioned, malignant growths, inflammatory states and pregnancy cause a pronounced rise; (3) as an index of the extent and intensity in pyogenic infections and (4) in estimating the activity of the inflammatory process in rheumatic fever.

CHAPTER VIII

THE SPLEEN; THE LIFE OF THE RED CELL; THE REGENERATION OF BLOOD

THE FUNCTIONS OF THE SPLEEN

The spleen serves three well recognized purposes, namely, (1) the final destruction of blood cells, (2) the storage of blood and (3) the manufacture of lymphocytes in the lymphoid tissue composing the Malpighian corpuscles (p. 55).

(1) THE RÔLE PLAYED BY THE SPLEEN IN THE DESTRUCTION OF THE BLOOD CELLS

In the pulp of the spleen are to be found relatively enormous mononuclear ameboid cells which have the power to engulf foreign particles of various sorts. They are known as *macrophages* and at times may be seen with fragments of, or even whole erythrocytes within their bodies. These cells belong to the reticulo-endothelial system (p. 78). In certain conditions in which a great destruction of red cells is a feature, immense numbers of these phagocytic cells may be seen loaded with erythrocyte fragments of various sizes. Sometimes merely a dust-like residue (*hemoconia*) containing hemoglobin is all that can be seen of the blood cell. Attempts to demonstrate a blood-destroying function of the spleen by comparative estimates of the corpuscular contents of the arterial (ingoing) and venous (outgoing) bloods have not, on the whole, been very successful. But Mann and his associates have been able, by spectroscopic examination of the arterial and venous bloods, to show a definite excess of bilirubin (iron-free pigment) in the blood of the splenic vein over that of the splenic artery. The bilirubin in the venous blood of other organs was no greater in amount than that in the arterial blood. In diseases with marked red cell destruction, the spleen becomes impregnated with iron and with an iron containing pigment, *hemosiderin*, derived from the hemoglobin of the disintegrated cells. Similar deposits occur in the liver and to a less extent in other tissues.

Though evidence derived from microscopical studies and from bilirubin estimations shows undoubtedly that red cell disintegration occurs in the spleen, it is believed that it is only fragmented, dead, or effete and senile erythrocytes that are disposed of in this way. The organ is not thought to attack healthy circulating cells. It rather

serves as a "grave-yard" than as a "slaughter-house" for the erythrocytes.

(2) THE SPLEEN AS A BLOOD-RESERVOIR

This function was discovered more or less by accident, and the discovery was a by-product, one might say, of researches which were being prosecuted with another aim in view. Barcroft and his party travelled to the Peruvian Andes to make observations upon the phenomena associated with acclimatization to high altitudes (mountain sickness). Blood volume and hemoglobin estimations were made upon the members of the party on board ship from time to time throughout the voyage in order that values at sea level might be obtained with which observations at the higher altitudes later could be compared. As the party reached tropical waters the blood volume as well as the hemoglobin concentrations were found to have increased. Upon passing the Equator and reaching colder regions these values declined again. It was surmised that the changes were due to temperature variations. It was difficult to conceive of a mechanism that could actually manufacture or destroy red cells at such a rate as to produce such rapid changes in blood volume and hemoglobin concentration. It was concluded, therefore, that the extra blood had been released, during the climatic rise in temperature, from some region where it had been stored, and was returned again to the reservoir when the temperature declined. The spleen was suspected of being the reservoir and subsequent experiments proved this to be so.

When guinea pigs were permitted to breathe an atmosphere containing from 0.06 to 1 per cent carbon monoxide, it was found that the blood of the general circulation contained the expected amount of the inhaled gas but the blood of the spleen contained none until a considerable time had elapsed. There was a lag in some cases of 2 hours in the absorption of the gas by the blood of the spleen. When, after the splenic blood had absorbed the gas, the animals were brought into pure air the carbon monoxide disappeared from the systemic circulation much sooner than from the blood of the spleen. These facts could only be accounted for on the assumption that blood had

been held in the spleen out of the general circulation, i.e., in a sort of cul de sac. No difference in the gas content of the bloods in the two regions occurred, however, if strenuous exercise were carried out immediately prior to the inhalation of the gas. This suggested that during exercise the spleen contracted, and expelled the blood that had been held stagnant within its substance. Proof was gained by an ingenious experiment. Metal rods were fastened to the spleen at such points that changes in their position would indicate changes in splenic volume. The animal's abdomen was closed and time allowed for it to recover after the operation. X-ray examinations were then made before and after exercise, when it was found that a pronounced shrinkage of the organ occurred as a result of the exertion. In other experiments the spleen was drawn out of the abdomen and fixed to the abdominal wall which was then closed around the splenic pedicle. The animal recovers after this operation and remains in good health. Direct observations of changes in splenic volume could by this means be made from time to time under different experimental conditions. It has been estimated that in the cat the spleen is capable of expelling during very strenuous exercise a quantity of blood (plasma and cells) equal to one-sixth of the total blood volume, and that the number of red cells discharged might be as much as one-fourth of the body's total supply. The blood of the spleen has therefore a much higher corpuscular content than that of the general circulation. The concentration of the blood in the spleen occurs very rapidly—within a few minutes.

By the liberation of a large number of red cells during exercise the blood is enriched in hemoglobin, and its oxygen carrying capacity as a consequence, increased. In this way the spleen serves an *emergency function*. Its value in an emergency was also shown when normal and splenectomized guinea pigs were exposed to an atmosphere containing a given percentage of carbon monoxide. The animals operated upon succumbed much sooner than the normal ones, and a dose just sufficient to kill the former was not lethal for the latter. There was no difference, however, in the survival time when hydrocyanic acid was used, since this poison does not cause death through any effect upon the oxygen carrying capacity of the blood. In conditions, such as muscular exercise, hemorrhage, carbon monoxide poisoning, etc., or under any circumstances in which the oxygen supply to the tissues falls below their requirements, contraction of the spleen and the expulsion of an

extra quota of blood into the circulation occurs. The necessity automatically brings about its own relief, for lowered oxygen tension is the adequate stimulus for splenic contraction. The stimulus evidently acts not directly upon the spleen but upon the nerve centers, for there is no response to lowered oxygen tensions if the splenic nerves have first been cut.¹

Cannon and Izquierdo have shown that in cats excitement produces an increase of over 25 per cent in the red cell count, which he ascribes to a discharge from the splenic reservoir. Injections of adrenaline, pituitrin, acetylcholine and pilocarpine have a similar effect. Hargis and Mann have demonstrated in dogs that the slightest disturbance in the animal's surroundings, e.g., the banging of a door, or procedures causing minor discomfort to



Fig. 16. Changes in volume of spleen as a result of emotional excitement (after Barcroft). Sketch on left, R, rest; C, dog sees cat. The numbers represent the relative sizes of the dog's spleen. Sketch on right, — . — . — rest; — — — smells cat; hears cat; — — — sees cat; — — — chases cat.

the animal, cause reflex-contraction of the spleen. This is accompanied by increased blood flow through the splenic vein.

The effect of emotional states upon splenic volume are shown in figure 16. The spleen also undergoes spontaneous rhythmical changes in volume which as shown by Barcroft and Nisimaru are responsible for certain low undulations seen in blood pressure tracings. These splenic contractions and the blood pressure waves to which they give rise have a duration of from 25 to 50 seconds (fig. 17). The blood pressure wave is the result

¹ It has been shown by Barcroft and his colleagues that the splenic volume progressively diminishes from about the middle of pregnancy to term. Blood is transferred apparently to the uterine vessels for the nourishment of the fetuses. After the birth of the young the spleen rapidly regains its usual size. In animals in which the spleen has been denervated, pregnancy does not cause a reduction in splenic volume.

of the slight increase in blood volume caused by the splenic contraction, the troughs of the splenic waves which represent the points of minimum splenic volume coinciding therefore with the crests of the waves on the blood pressure tracing. The waves are more pronounced after denervation of the spleen; they disappear after clamping the splenic artery.

The structure of the spleen is suited most admirably for the two functions which have just been considered. In its relaxed condition in the living body it is a large organ—3 to 5 times larger than post-mortem examination would lead one to expect, for the throes of death cause it to contract to minimal proportions. The blood is delivered into the substance of the spleen by fine arterial vessels. Through these the blood floods the

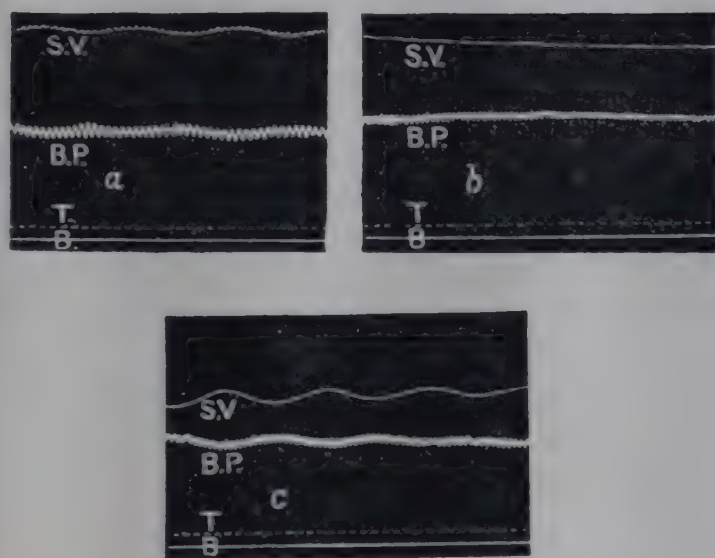


FIG. 17. S.V. = splenic volume. B.P. = general arterial blood pressure. T = time, 5 sec. B = baseline at 40 mm.Hg. Spleen in plethysmograph; *a*, before clamping splenic vessels, *b*, after clamping vessels, *c*, after removal of clamp (after Barcroft and Nisimaru).

splenic pulp and percolates between its cells. It is collected again into venous sinuses whose walls are formed of flattened cells possessing phagocytic proclivities of the highest order (reticulo-endothelial elements). The blood passes freely into the sinuses through numerous perforations in their walls. A certain proportion of the splenic arterioles open directly into the sinuses. The latter are drained by small veins with intact walls which join with similar radicles to form larger venous trunks. The splenic circulation is therefore an open one and a large part of the blood in its passage from the arterial to the venous side traverses the morass of splenic pulp. The flow at ordinary times is very sluggish, and within the venous sinuses the blood may be almost stagnant. Nevertheless within a relatively short time all the red cells in the body are brought into direct relationship with the splenic tissue to pass inspection by the macrophages lurking in the pulp and

lining the sinuses. To these cells the infirm, senile or dying erythrocytes fall a prey.

The capsule of the spleen is provided with *unstriated muscle* fibers which penetrate its substance and are continued along the fibrous trabeculae into the depths of the organ. The distribution of the muscle in this way explains how the spleen is enabled so quickly to alter its volume.

Dotted throughout the spleen, like islands, and surrounded by the pulp are lighter areas of lymphoid tissue. These are the *Malpighian corpuscles*. Many of them, especially in infancy, show a pale central area known as the "germ center." The Malpighian corpuscle (fig. 18) is pierced by a small artery; it is analogous to



FIG. 18. Diagram of the human spleen. (A) artery and vein (V) in a trabecula (T) of the capsule (C); ZA, central artery of the corpuscle of Malpighi (MK); P, small arteries; HA, arteries with a sheath; AK, arterial capillaries which terminate in the sinuses (I) or in the meshes of the reticulum (2); MS, venous sinuses; W, white pulp (from Cajal after Szymonowicz).

similar areas in lymph nodes, and serves the same function, namely the manufacture of lymphocytes. The development of these cells is considered in Chapter XI.

ENLARGEMENT OF THE SPLEEN (SPLENOMEGALY)—SPLENECTOMY

Removal of the spleen in animals as a means of studying its functions with regard either to blood destruction or to blood formation has yielded little definite information. The organ does, however, appear to have an indirect influence upon blood destruction in that it alters the resistance of the red cells to the action of hypotonic solutions and other hemolytic agents. If

the spleen be removed, the erythrocytes are rendered much less fragile as is shown by the reduced power of certain poisons to cause hemolysis. The spleen appears also, under certain conditions at any rate, to cause excessive destruction of blood platelets and even in persons with a normal blood picture splenectomy causes an increase in platelets. The erythrocytes of the blood in the spleen are also more fragile than those of the general circulation.

In *purpura hemorrhagica* (p. 95) removal of the spleen is followed by a rise in the platelet count and amelioration of the symptoms. Also, substances such as anti-platelet serum or diphtheria toxin, which when injected cause platelet destruction, are rendered much less effective if the spleen has been removed. Splenectomy frequently brings about a cure in *hemolytic jaundice* (acholuric jaundice) p. 61. The spleen may be considerably enlarged in *pernicious anemia* but splenectomy exerts no effect upon the course of the disease and is never justified. (It has been mentioned that the spleen does not destroy healthy erythrocytes and the fragility of the red cells is actually decreased in *pernicious anemia*.) In *splenic anemia* (Banti's disease), the spleen is tremendously enlarged, the liver becomes cirrhotic, there are repeated hemorrhages. Splenectomy has been practised with success in this condition. Splenic enlargement is a feature of many other abnormal conditions, such as malaria, Hodgkin's disease, leukemia, etc., but in these benefit does not follow its removal. The organ is also enlarged sometimes enormously in *polycythemia*, but splenectomy fails to cure the condition, and indeed is attended by grave risks to life (Moynihan).

Gaucher's disease is an interesting though rare condition which, commencing usually in childhood, is associated with a colossal enlargement of the spleen. The enlargement is due to hypertrophy and hyperplasia of reticulo-endothelial elements. Masses of very large vesicular cells (Gaucher's cells) filled with a cerebroside called *kerasin* are seen in the lymphoid tissue and venous sinuses of the spleen. Hyperplasia of reticulo-endothelial elements also occurs in other situations, e.g., bone marrow and liver. The disease is due apparently to some disorder of lipid metabolism. Splenectomy is the only effective treatment. *Niemann-Pick's disease* is a somewhat similar condition affecting the reticulo-endothelial system and lipid metabolism. Characteristic cells, known from their appearance as "foam cells," are present in large numbers; they are loaded with an unknown phospholipid material. Subjects of this and the preceding disease are usually children of the Jewish race. *Von Jaksch's disease* occurs in infants and is characterized by splenomegaly, anemia and an increase in the number of white blood cells.

From its position in the portal circulation the spleen is also very susceptible to enlargement, either as a result of mechanical obstruction to the veins or to high venous pressure resulting from cardiac or hepatic disease.

THE LIFE OF THE RED CELL

From the amount of bile pigment which is excreted daily by the liver the conclusion must be drawn that a very large amount of hemoglobin (since this is the sole or at least the main source of bile pigment (p. 459)) is liberated from disintegrated red cells in 24 hours.

There are three possible ways in which erythrocytes might be destroyed in the body: (1) By the macrophages of the spleen, (2) by the action of a hemolytic substance in the blood, (3) through simple wear and tear and disintegration in the blood stream. There is no evidence that hemolysis occurs to any significant extent in normal blood and the phagocytic cells of the normal spleen seem quite inadequate to account for the wholesale destruction of cells which evidently must be going on continually in the body. The work of Rouse indicates that the erythrocytes to a very large extent undergo disintegration in the blood stream as a result of the stresses and strains to which they are incessantly subjected during their passage through the vessels. When it is considered what a delicate structure the red cell is and to what violent treatment it is exposed during its lifetime, this wastage is not surprising. The cells are flung from the heart into the arteries at high velocity. In their voyage around the circulation they are exposed to jostlings and innumerable collisions with one another and with the arterial walls. At times they are forced through channels which are too narrow to permit their passage without marked distortions of their shape; or they may be caught in a fork at the branching of a vessel and become "saddle-bagged" over it. Their membranes are almost continually undergoing alterations in tension as a result of osmotic changes. At last becoming older they are unable to withstand these abuses and undergo fragmentation. Fragments of different shapes and varying in size from that of a half or a quarter of the whole cell, to mere dust-like remnants containing hemoglobin (hemoconia) may be found in the circulating blood, in the spleen and to a limited extent occasionally in other tissues.

It has been estimated that in health about ten million cells are destroyed in this way every second—and of course the same number must be formed afresh by the blood forming tissue. The loss of hemoglobin is about 25 grams daily. The number of red cells and hemoglobin concentration in the circulation at any moment represents the balance struck between blood wastage and blood formation by the bone marrow.

Many attempts have been made to determine

the life-span of the erythrocyte. Ashby used an ingenious method for such determinations in man. This method consists in transfusing compatible red cells into an individual and later examining his blood from time to time for the presence of the foreign corpuscles. The foreign cells are distinguished from the transfused person's own cells by means of the serum of another belonging to a group with which the recipient's cells but not the foreign cells are incompatible² (p. 34). Using this method, it has been found that the life of the average red cell is about 80 days and some survive for over 120 days. The life of the erythrocyte of the dog has been estimated by Hawkins and Whipple at 124 days.

THE REGENERATION OF BLOOD

THE MATERIALS NECESSARY FOR ERYTHROCYTE FORMATION

(a) *The red cell stroma.* It is doubtful whether the materials required for the construction of the framework of the cell, e.g., nucleoprotein, globulin, lecithin and cholesterol are ever lacking. The body possesses large supplies of these materials and an ordinary diet contains them in adequate amounts.

(b) *Hemoglobin* is added to the red cell only after the cell's development has progressed to a certain stage (p. 83). The complete history of hemoglobin in the body has yet to be written, but the researches of Whipple and his associates indicate that the body can synthesize the pyrrol nucleus for the manufacture of the blood pigment. When hemoglobin was given intravenously to anemic dogs, the animals' hemoglobin was increased by an amount equal to that injected. At the same time the excretion of bile pigment was increased by a corresponding amount. This apparently paradoxical result is interpreted in the following way. The pyrrol of the injected hemoglobin is excreted as bilirubin, while the globin part of the molecule is utilized for the production of new hemoglobin, the pyrrol groups of which must therefore be derived from some other source—food or body tissue—and synthesized to porphyrin. It is possible that food porphyrins differing from that in hemoglobin can be broken down into their constituent pyrrol groups which are then rebuilt into proto-

² Thus if corpuscles of Group O are transfused into a person belonging to Group A or AB then, when the recipient's blood is mixed outside the body with Group O serum, the recipient's corpuscles but not the foreign cells will be agglutinated.

porphyrin (p. 40). The supposed value of spinach and other green vegetables as hemoglobin builders has suggested such a process. Yet according to Whipple and his associates chlorophyll is not utilized by the dog for hemoglobin synthesis.³ It has already been pointed out (p. 41) that heme (porphyrin + iron) is a universal material and is present in the great majority of food stuffs. So here it might be supposed was a source of an almost unlimited supply of the necessary pigment element. Yet this compound cannot be split by the digestive secretions and it is generally agreed that iron so combined can not be utilized for hemoglobin

TABLE 9
Hemoglobin production influenced by diet

DIET, GRAMS DAILY	HEMOGLOBIN PRODUCTION (TWO-WEEK FEEDING PERIOD)
	grams
Bread 400.....	3
Milk 450, Bread 400.....	3
Cream 100, Bread 400.....	10
Butter 100, Bread 350.....	15
Asparagus 200, Bread 300.....	9
Spinach 200, Bread 300.....	15
Raspberries 200, Bread 300.....	5
Raisins 200, Bread 300.....	25
Apricots 200, Bread 300.....	48
Eggs 150, Bread 300.....	45
Whole fish 250, Bread 300.....	13
Beef muscle 250, Bread 300.....	17
Pig muscle 250, Bread 300.....	30
Chicken gizzard 250, Bread 200.....	80
Kidney 250, Bread 300.....	70
Chicken liver 250, Bread 300.....	80
Beef liver 300, Bread 300.....	80
Beef liver 450.....	95

synthesis. The globin necessary for the completion of the hemoglobin molecule is available in most meats, and Whipple and his associates have found that this protein is well utilized for hemoglobin synthesis, yielding for each 100 grams fed from 30 to 40 grams of blood pigment. Hemoglobin or globin or a digest of the latter when given intravenously forms hemoglobin almost gram for gram. They found that as compared with the

³ Hughes and Latner found that whereas large doses of chlorophyll do not favor hemoglobin regeneration, small quantities (15 mgm.) are definitely stimulating. The larger doses they believe exert a toxic action (possibly due to the magnesium content of the pigment) upon the bone marrow.

porphyrin part of the molecule globin was of much greater importance for hemoglobin regeneration; globin apparently is a limiting factor in hemoglobin synthesis. Upon a diet low in protein but adequate in iron hemoglobin regeneration was minimal. Certain amino-acids, especially proline and threonine were found to increase hemoglobin regeneration above the basal level, which suggests that they are used for the synthesis of globin. Histidine which constitutes 8 per cent of the globin molecule is, contrary to expectation, less effective.

Whipple, Hooper and Robschait carried out a series of experiments upon animals made anemic through repeated bleedings, and tested their power to regenerate hemoglobin when fed upon various diets. Meats were found to be the most potent for this purpose. Carbohydrates in the form of bread and sugar were found to be ineffective. In fact they had actually a definitely depressing effect upon the hemoglobin repair process, for animals regenerated their blood more rapidly when starved than when fed upon a bread and sugar diet. In explanation of this fact Whipple suggested that the starved animal drew upon its tissues to supply the basic elements for hemoglobin synthesis, whereas carbohydrate food on account of its well-known protein-sparing effect (p. 553) prevented the tissues from being utilized in this way. Infection or very severe liver damage markedly depresses hemoglobin regeneration in anemic dogs. The depressing effect upon regeneration of hemoglobin which is seen in the bile and Eck fistula animals is apparently due to interference with liver function (defective protein synthesis) and to the reduction in iron absorption.

These workers found that, of all protein foods, liver was by far the most effective for blood regeneration. Next in order came kidney and chicken gizzard. Milk had little regenerating effect. Table 9 shows the comparative values of the various articles of diet. A bread mixture consisting of potato and wheat flour, bran, sugar and the necessary salts and vitamins was used as the basal diet. This was practically inert so far as the regeneration of hemoglobin was concerned. The article to be tested was added to this basal diet.

The animals (dogs) were rendered anemic by three or four successive bleedings until the hemoglobin had been reduced to 30 per cent of the normal. The animal was then placed upon the diet to be tested, and was bled from time to time in order to maintain the hemoglobin at the original level of 30 per cent. The amount

of blood removed expressed in grams of hemoglobin gave a direct measure of the amount of pigment regenerated in a given time.

Cobalt has a powerfully stimulating effect upon red cell production and in repeated doses may induce polycythemia (p. 10).

The clinical application of these laboratory findings will be considered in the next chapter.

IRON METABOLISM

Being an essential constituent of the hemoglobin molecule, this mineral must be available in adequate amounts in order that normal blood regeneration shall occur. A diet deficient in iron leads to a certain type of anemia. Iron provides the keystone for hemoglobin construction; unless it is supplied in appropriate amounts the maturation of the red cells is retarded, and the numbers discharged from the bone marrow into the general circulation, reduced.

Absorption, storage and excretion of iron

Iron is absorbed throughout the entire intestinal tract, but to the greatest extent in the upper part of the small intestine. The absorption is by way of the blood. After absorption the metal disappears rapidly from the circulation, being stored in the liver and to a less extent in the spleen and kidney. Liver iron is readily increased by iron feeding or injection. Only minute quantities of iron are detectable in the plasma (0.1 to 0.3 mg. per 100 cc.) under ordinary circumstances, the great proportion of the iron of the body being present in the red cells. A smaller quantity is present in the muscle (myoglobin, cytochrome, etc.). Whole blood contains from 45 to 50 mg. per cent and the total quantity in the adult human body is about 4 grams. Iron is present in the blood in three forms, (a) plasma iron, already mentioned and which represents mainly iron in transit from the intestinal tract to the depots, (b) iron combined with hemoglobin, which accounts for from 92 to 98 per cent of the total, and (c) from 2 to 8 per cent which is liberated by the action of mineral acids and called for this reason "easily split off" iron. This fraction is attached to the erythrocyte, and is derived apparently from an intermediary compound formed in the breakdown of hemoglobin.

It is commonly stated that iron is excreted almost exclusively through the intestinal wall, mainly through the wall of the colon. The evidence for this statement is not, however, very

convincing. If it were true one would expect an increase in fecal iron in conditions associated with the excessive breakdown of red cells, which is not the case. Also when iron is injected into rats almost all can be recovered from the organs, none appearing in the feces. Only very minute amounts of iron appear in the urine and bile and it is probable that correspondingly small quantities are excreted by the bowel. According to McCance and Widdowson, the iron content of the body is controlled through the *regulation of absorption* and not by excretion. Several factors influence iron absorption, e.g., the acidity of the gastric juice and especially the *reserve stores of iron* in the body. Balfour and his associates found, for example, that from 2 to 10 times the usual quantity of radioactive iron⁴ was absorbed in the later months of pregnancy when the iron stores are low. The absorption of iron is increased by chlorophyll, by bile pigments, by calcium and by vitamin C, and diminished by excessive secretion of mucus. Iron is therefore largely a "one-way" element. It is absorbed, the absorption being conditioned by several factors, but, under ordinary circumstances, it is excreted only in minute amounts.

Besides its well known function as an essential element in the hemoglobin molecule, and as a constituent of other respiratory pigments, iron appears to play a rôle in the nutrition of epithelial surfaces. Abnormal nail growth, glossitis, fissures around the corners of the mouth and localized thickening of the mucous lining of the esophagus leading to dysphagia occur in anemias due to iron deficiency, and are cured by iron administration.

Fifteen to twenty milligrams (p. 668), is the daily iron requirement of the adult.

The erroneous belief has been current in the past that only iron in organic combination could be absorbed and utilized for the construction of hemoglobin. Whipple and associates found that in the posthemorrhagic anemia of dogs iron in any soluble form was utilized, and Elvehjem, Hart and Sherman found that inorganic iron in the form of ferric chloride, pyrophosphate, hypophosphite and glutamate was utilized. The idea that only organic iron is available for hemoglobin synthesis probably arose from the fact that in iron-containing foods (e.g., egg-yolk) which were recognized to be efficient hemoglobin formers, the inorganic iron is

masked. It is now known that the truly organic iron of such foods, namely that combined in heme, is not available, since it is not released by peptic or tryptic digestion, whereas the inorganic iron which may represent 50 per cent or more of the total iron of the food is utilizable. This latter after conversion to the ferrous form is estimated by the dipyrindyl method. During digestion the inorganic iron of the food, which is in the ferric state, gives up oxygen to oxidizable substances in the alimentary tract and is converted, in part at any rate, to the ferrous state; as such only is it absorbed. Animals fed dipyrindyl become anemic since the ferrous iron is rendered insoluble.

In certain anemias, especially when the gastric juice lacks HCl, which normally aids in the liberation of iron from the food, and facilitates its conversion to the ferrous form, compounds of ferrous iron, e.g., ferrous chloride⁵ and ferrous carbonate are specific in their effects, causing a discharge of reticulocytes from the bone marrow and an increase in the red cell count.

THE SIGNIFICANCE OF COPPER

This metal is believed to act as a catalyst in some stage of hemoglobin synthesis. It does not itself enter into the structure of the hemoglobin molecule. Waddell, Elvehjem, Steenbock and Hart found that in young rats rendered anemic by being placed upon a diet of whole cow's milk, iron alone failed to promote hemoglobin regeneration.⁶

⁵ Ferric iron, e.g., reduced iron or iron and ammonium citrate, must be given in relatively very large amounts since only a small proportion of it is converted to ferrous iron in the gastro-intestinal tract. When reduced iron is dissolved in dilute hydrochloric acid, ferrous chloride is formed. The administration of a mixture of this sort has been strongly advocated by Lucas and Henderson (Can. Med. Ass. Jour., 1933, 28, 298).

Iron is sometimes given parenterally but it is to be remembered that when free in the blood stream the metal exerts a toxic effect. The lethal dose for an animal is 30 to 60 mg. per kilogram. It has been shown by Castle and associates that in hypochromic anemia a daily dose of 32 mg. of iron in the form of iron and ammonium citrate, administered parenterally, is utilized completely in the formation of hemoglobin. It was also shown that 32 mg. of iron administered in this way is equal to 1000 mg. given by mouth. This is merely a further demonstration of the fact that only a very small proportion of ferric iron is converted into the absorbable form in the alimentary tract and should not be taken in any way to imply that iron administered by injection has any advantage over ferrous compounds given in adequate amounts by mouth.

⁶ Some experimenters have obtained a certain degree of hemoglobin regeneration with iron alone, though the rate of regeneration was much increased by the addition of copper.

⁴ Radioactive iron has proved a valuable tool in studies of iron metabolism since it can be readily traced in the body tissues and fluids. It is prepared by bombardment of Fe⁵⁸ isotope with deuterium.

When the iron was supplemented by a very small quantity of copper, blood regeneration was induced. Manganese exerts a similar though less pronounced supplementary effect. The liver is the main storehouse for copper and minute amounts (0.1 to 0.5 mg.) are present normally in blood.

Though anemia due to copper deficiency is unknown in man, a severe and even fatal anemia due to the lack of this metal may occur in farm animals, e.g., the "falling sickness" of South African cattle.

Hemochromatosis

This is a disturbance in iron metabolism in which extensive deposits of an iron-containing pigment called *hemosiderin* are found in the liver and other tissues. The Kupffer cells (p. 80) are loaded with pigment. Deposits are also found in the parenchymal cells. The disease is not due, as was believed at one time, to

increased blood destruction. The total iron content of the body is greatly increased; it may be 10 times the normal amount. A second yellow iron-holding pigment known as *hemofuscin* is also sometimes present in the connective and muscular tissues. Other features of the condition are *bronzing of the skin*, *cirrhosis of the liver*, *sclerosis of the pancreas* with diabetes (bronzed diabetes). The cause of the condition is unknown, though it has been ascribed by Mallory to chronic copper poisoning. According to this observer the excretion of iron is interfered with; the hemoglobin liberated, as a result of the normal wastage of red cells, combines with copper to form *cuprohemol*. The foreign metal is later freed and hemofuscin formed. This is then converted by tissue enzymes to hemosiderin which induces necrosis and fibrosis of the tissue at the site of its deposition.

Hemosiderosis is the term applied to the deposit of hemosiderin in the tissues which occurs as a result of the excessive breakdown of red cells in malaria and hemolytic types of anemia. It may be looked upon simply as an exaggeration of the normal process of iron deposition.

CHAPTER IX

THE ANEMIAS

CLASSIFICATION

We have seen that in health the population of red cells and the concentration of hemoglobin in the blood are kept at normal levels by a nice balance between the new formation and the wastage of erythrocytes. Anemia results when the balance is tipped one or the other way, i.e., by a defect of blood formation or an increase in blood wastage. So the anemias may be classified broadly into (A) *those associated with blood loss or increased blood destruction* and (B) *those due to defective blood formation*.

(A) *Anemias due to blood loss or increased blood destruction*. Among this group are included those types of anemia resulting from:

- | | |
|--------------------------|---|
| Post-hemorrhagic anemias | (a) Hemorrhage |
| | <ul style="list-style-type: none"> i. Acute ii. Chronic, as a result, for example, of peptic ulcer, uterine bleeding, ankylostomiasis (hook-worm disease) purpura, etc. |
| Hemolytic anemias | (b) Red cell destruction, as a result of: |
| | i. Chemical hemolytic poisons, lead, arseniureted hydrogen and certain coal tar derivatives. |
| | ii. Specific infections, e.g., malaria, septicemia. |
| | iii. Abnormal structure of the red cells, e.g., hemolytic or acholuric jaundice and sickle cell anemia. |
| | iv. An auto-agglutinin or endogenous hemolysin of unknown nature, e.g., paroxysmal hemoglobinuria (p. 50) and the acute hemolytic anemia of Lederer. |

In the hemolytic group the increased blood destruction is manifested by a rise in the concentration of bile pigment in the plasma which gives an indirect van den Bergh reaction (p. 465), a greater excretion of pigment in the urine (urobilin) and feces, and the deposit of an iron-containing pigment in the liver and other tissues (hemosiderosis, p. 60). There is frequently jaundice of a slight or moderate grade.

Sickle-cell anemia is believed to be due to blood

destruction as a result of a congenital anomaly of the red cells. In this type which occurs almost exclusively in negroes, elongated crescent or sickle-shaped erythrocytes some 15μ or so in length are a characteristic feature. Such cells are found in the blood of a high percentage of negroes (8 to 9 per cent) though only relatively few, 1 in 40, of these develop anemia.

Hemolytic or acholuric jaundice. The chief features of this form of anemia are a *familial tendency*, *jaundice* and high incidence of pigment gall stones, *spheroid erythrocytes* (i.e., the diameter of the cells is reduced but their thickness increased, their volume being approximately normal), *reticulocytosis* up to 60 per cent or more of the total red cell population, increased *fragility* of the cells and *enlargement of the spleen*. Splenectomy is usually followed by the disappearance of jaundice, a return of the red cell count to normal and a marked reduction in the reticulocytosis. The spherocytosis gradually disappears and with it the increased fragility of the erythrocytes. These facts indicate that disordered function of the spleen is not the primary cause of the condition. The cause of the hemolysis is unknown though it may be due simply, as in certain other anemias, to the reaction of the macrophages of the spleen to the defective cells produced by an abnormally functioning bone marrow. Others believe that an endogenous hemolytic agent is responsible, a view which receives support from the experiments of Dameshek and Schwartz in which a hemolytic serum produced by the injection of guinea-pig's cells into rabbits was employed to produce anemia. The injection of this anti-guinea-pig hemolytic serum into guinea-pigs caused a profound drop in the red cell count and the appearance of cells with spheroid shape, increased fragility and a reticulocytosis. These observers believe that the greater fragility of the red cells is simply a function of their increased thickness and that spherocytosis is the primary change—a reaction of the bone marrow to excessive destruction of red cells caused by a circulating hemolysin.

(B) *Anemias due to defective blood formation*. This group comprises anemias resulting from:

- (a) *Nutritional anemias*. i. *Iron deficiency*—hypochromic, microcytic anemias. The deficiency may be due either to the excessive loss of iron from the body as in chronic hemorrhage or to an inadequate quantity of this element in the diet (p. 62).
- ii. *Protein deficiency*, though in itself a less common cause of anemia, is not infrequently a contributory factor. iii. *Lack of vitamin C* or of certain factors of the *B complex*, e.g., pyridoxin.

- (b) *Lack of or failure in the utilization of the specific anti-anemic factor*—Addisonian pernicious anemia and certain related hyperchromic macrocytic anemias with a megaloblastic type of bone marrow (p. 64).
- (c) *Macrocytic anemias (hypo- or hyperchromic) with normoblastic bone marrow.*
- (d) *Toxic agents which induce aplasia of the bone marrow or depress its function—aplastic anemias.* Among such agents are benzol, arsphenamine, radium, X-rays and sometimes bacterial and syphilitic toxins. This is the most severe type of anemia. The red marrow is greatly reduced in amount, being replaced by fatty tissue. Blood formation is profoundly depressed. Anemia of the aplastic type may also result from exhaustion of the bone marrow following a long period of overactivity induced by some other type of anemia, or may appear without a known cause (*idiopathic aplastic anemia*, p. 69).

The anemias associated with certain conditions, e.g., nephritis and chronic infections, are believed to be due to a relatively mild degree of depression of bone marrow function. In such types, destruction of red cells by toxic substances (metabolic or bacterial) may also be a contributory factor.

The cause of *splenic anemia* (Banti's) is unknown; it is therefore difficult to fit this type into either of the preceding categories. According to some there is increased blood destruction, but the chief factors appear to be depressed marrow function and the loss of blood resulting from repeated gastro-intestinal hemorrhages. An anemia very closely resembling Addisonian or true pernicious anemia results from infestation with the fish tapeworm, *Diphyllobothrium latum*. A toxin derived from the worm itself is a factor but apparently not the sole one in the development of the anemia. It is exceedingly rare on this continent.

The following indices calculated from the hemoglobin concentration, red cell count and cell volume of a specimen of blood are employed to express the characters of the individual cells in the different types of anemia.

The *color index*. This is a numerical expression of the hemoglobin content of the individual red cells. It is obtained by dividing the hemoglobin value in grams per 100 cc. by the red cell count, both values being expressed as percentages of the normal. (The normal weight of hemoglobin per 100 cc. is taken as 14.5 grams and the red cell count as 5 million.) Thus, if the hemoglobin is 60 per cent of normal and the red cell count 50 per cent, then $\frac{60}{50} = 1.2$ color index. But if the hemoglobin percentage is reduced to a greater degree than the red cell percentage the index will be

less than unity. That is, each red cell contains less than its normal quota of hemoglobin. On the other hand, the hemoglobin concentration of the blood may be greatly reduced but if the reduction runs parallel with the reduction in red cell percentage the index will have the normal value of 1.0.

The *iron index* is obtained by dividing the number of milligrams of iron in 100 cc. of blood by the first three figures of the red cell count. The normal value is between 9.50 and 10.00. Thus if there are 50 mgm. of iron in 100 cc. of blood and the red cell count is 5,000,000, the iron index is $\frac{50}{5.00} = 10.00$. Sometimes

what is known as the *iron color index* is employed. This is the quotient obtained by dividing the iron content expressed as a percentage of the normal by the percentage of red cells. Thus

$$\frac{\text{Percentage of iron}}{\text{Percentage of red cells}} = \text{iron color index}$$

The *volume index* is an expression of the average size of the red cells in a given sample of blood as compared with the average normal size. It is obtained by dividing the volume of the red cells (as determined by the hematocrit and expressed as a percentage of the volume of a healthy person) by the number of red cells as a percentage of the normal, (the normal being taken as 5 million). Thus, if the volume of cells in the sample is 40 cc. per 100 cc. of blood, i.e. 90 per cent of the average normal volume (which is 45 cc.) and the red cell count is 4.5 million, which is also 90 per cent of the normal, then the volume index is $\frac{90}{90} = 1$. If, on the other hand, the volume is say 70 per cent of the normal and the red cell count 50 per cent then $\frac{70}{50} = 1.4$ volume index. That is, the average size of the red cells is greater than normal.

The *saturation index*. This is an expression of the concentration of hemoglobin in the red cell and is obtained by dividing the figure for the weight of hemoglobin by the figure for the packed cell volume, both figures being percentages of the normal. Thus, if the weight of hemoglobin is 11.6 grams per 100 cc. (i.e., 80 per cent of normal) and the packed cell volume is 40 (i.e., 88 per cent of normal which is taken as 45) then, $\frac{80}{88} = 0.90$ saturation index.

HYPOCHROMIC MICROCYTIC ANEMIAS—IRON DEFICIENCY

In this group the essential defect is one of hemoglobin formation. The hemoglobin percentage of the blood is reduced to a greater extent than the number of red cells. These, indeed, may show only a slight reduction. The color index is therefore considerably below the normal, which means that each red cell has received less than its normal

quota of pigment. The erythrocytes are also smaller than normal, so the volume index is also low. The low color index is in part the result of the smaller size of the red cell but also of a reduced concentration of pigment throughout the red cell's substance. The saturation and iron indices are therefore also lowered. Some of the corpuscles are so pale that they resemble "ghosts" (p. 48) or only the peripheral zone of the cell is colored (anisochromasia). (See figs. 19 and 20, and frontispiece.)

Iron deficiency is considered to be the essential cause of the anemias belonging to this class. The deficiency may result from an inadequate amount of iron in the diet or from defective absorption of the metal from the food.

Chlorosis is a type of hypochromic anemia which until the last 40 years or so was commonly seen in girls and young women between the ages of 16 and 22 years. It received its name from the peculiar greenish pallor of the skin (green sickness). There was usually hyperchlorhydria. The disease is now rare possibly owing to the more adequate diets of the present generation.

HYPOCHROMIC ANEMIA WITH HYPOCHLORHYDRIA OR ACHLORHYDRIA (ALSO CALLED IDIOPATHIC HYPOCHROMIC ANEMIA)

Some believe that the failure of gastric function is the primary cause of this type. The hydrochloric acid of the gastric juice is normally an important factor in the liberation of iron from the food and in its conversion to the ferrous state. These are necessary preliminaries for its absorption. According to Davidson and Leitch the hypochlorhydria is merely an accessory factor in the production of the iron deficiency, the iron intake being also below the normal. In the experience of these observers, the diets of patients showing this variety of anemia were poor in first class protein, milk and vegetables and contained about half the minimal daily iron requirement of from 15 to 20 mgm. Repeated small hemorrhages or excessive menstrual losses are often contributory factors. It is seldom that one or more of the causes enumerated cannot be detected and for this reason the title "idiopathic" as applied to this type of anemia is scarcely appropriate. Hypochromic anemia sometimes follows operation for the removal of a large section of the stomach.

HYPOCHROMIC ANEMIA WITHOUT HYPOCHLORHYDRIA

Hypochromic anemia with normal gastric acidity also occurs and like the preceding is due to iron deficiency. It occurs most frequently in women

of childbearing age when the dietary deficiency is aggravated by the losses of iron incident to menstruation or repeated pregnancies. Davidson has recently emphasized the need for larger amounts of iron during this period in women.

ANEMIA OF INFANTS

The fetus accumulates a store of iron in the liver in the later months of gestation which serves as a reserve which is drawn upon for the manufacture of hemoglobin in infancy. The high red cell concentration (p. 8) with which the infant comes into the world also contributes to the iron reserves. In the normal infant the iron stores are sufficient for the manufacture of hemoglobin for the first six months or so. Growth, however, makes heavy demands upon the iron supplies and after the first half year it is necessary to provide a diet which will contain adequate amounts of iron in order to guard against the development of anemia of the hypochromic type. Milk, it will be recalled, is very poor in both iron and copper. The development of anemia in milk-fed rats has been mentioned and the anemia of sucklings is a problem in the breeding of farm animals. If the iron stores are deficient at birth as in premature infants or as a result of maternal anemia, anemia may occur in the very young infant.

The hypochromic anemias respond in a spectacular fashion to the administration of inorganic iron (e.g., ferrous chloride, ferrous carbonate, etc., see p. 59). The administration of copper is rarely necessary since this occurs in sufficient quantity in the diet and as an impurity in iron preparations.

PERNICIOUS ANEMIA (ADDISON'S ANEMIA) AND RELATED MACROCYTIC ANEMIAS

Pernicious anemia is due essentially to a defect in the formation of the red cells; hemoglobin synthesis is unaffected.

The CHIEF FEATURES of the blood picture are:

(1) *Great reduction* in the number of red cells and consequently in the hemoglobin percentage. The blood count in a very severe case may be no more than 10 per cent of the normal.

(2) The red cells are reduced in number below the normal to a greater extent than is the hemoglobin percentage. The *color index* is therefore *raised* above normal as are also the saturation, iron and volume indices.

(3) Large cells—the average diameter of the cells is increased to between 8 and 9 microns and exceptionally large cells called *macrocytes* are plentiful. The average volume of the individual red cells (figs. 19 and 20) is

about 135 cu. microns (normal about 90 cu. microns). *Normoblasts* and *megaloblasts* may also be seen. The reticulocytes are around 3 per cent.

(4) The total number of leucocytes is reduced but the lymphocytes are relatively increased.

(5) Great variation in the size of the cells—*anisocytosis*, the cells varying from those smaller than normal to the large cells mentioned above. *Poikilocytes* are moderate in number.

(6) Increase in iron and bilirubin of the plasma; increased excretion of pigment (urobilin)—indirect van den Bergh.

(7) Blood volume reduced mainly as a result of the red cell diminution, the plasma volume being around the normal level.

(8) Fragility of the red cells usually slightly reduced.

OTHER FEATURES.

(1) The red bone marrow is hyperplastic. It extends into the shafts of the bones displacing the yellow marrow and even the bony walls may be eroded. Upon microscopical examination the marrow shows megaloblasts and other immature forms in large numbers (see p. 84).

(2) Achlorhydria almost always exists.

(3) Sore tongue—*glossitis*.

(4) Chronic combined degeneration of the cord.

(5) Urobilin appears in the urine in severe cases; and in all those in which plasma bilirubin is increased urobilinogen is in excess in the feces. In health from $\frac{1}{140}$ to $\frac{1}{340}$ of the total amount of hemoglobin in the blood is excreted daily as urobilinogen. In pernicious

anemia $\frac{1}{10}$ of the total hemoglobin may be excreted as urobilinogen. Hemosiderin deposits (p. 60) occur.

(6) The disease shows remissions and relapses. During the remissions, the blood picture approaches the normal and the percentage of reticulocytes increases—*blood crises*. During the relapses, the characteristic hematological features of the condition are exaggerated.

The essential factor in the production of pernicious anemia is not believed to be increased blood destruction, but rather a defect in blood formation—the reversion of the bone marrow to a more primitive type of erythropoiesis (see p. 83). Increased blood destruction undoubtedly occurs as evidenced by the rise in plasma bilirubin but it is a secondary effect. The abnormal erythrocytes probably stimulate the phagocytic activities of the reticulo-endothelial cells (p. 78) in the spleen, liver and elsewhere. Since the fragility of the red cells is reduced rather than increased it would not appear that they disintegrate more readily in the blood stream (see p. 56). The discovery of an anti-anemic principle in liver and subsequent re-

searches arising from the employment of this principle in the treatment of pernicious anemia has shed a flood of light upon the nature of the disease.

TREATMENT WITH LIVER, LIVER EXTRACT AND GASTRIC TISSUE

In 1926 Minot and Murphy inspired by the laboratory finding of Whipple and his associates, namely, that liver was the most effective article of diet for the treatment of anemia in dogs, tried the effect of adding liver to the diet of pernicious anemia patients. The spectacular success which followed this treatment is well known and today lightly cooked liver (from $\frac{1}{2}$ to 1 pound per day) or liver extract is recognized as a specific for the disease. Kidney tissue was shown to have a similar though less pronounced curative effect. The anti-anemic (or hematinic) principle is contained in the non-protein fraction of liver. Its chemical nature is not known precisely¹ but it is free from lipids, protein and iron. The extract may be given by mouth or intramuscularly. Its action is more rapid and at least 30 times more potent when given by the parenteral route. It may be mentioned here that Wilkinson found that the anti-anemic principle was present in normal human liver and in the livers of pernicious anemia patients who had received specific treatment, but was absent from the livers of untreated subjects of the disease.

The production of the anti-anemic principle, gastric (intrinsic) and extrinsic factors

As already mentioned, achlorhydria is an almost invariable accompaniment of pernicious anemia. The significance of this fact was demonstrated in

¹ Dakin and West reported a few years ago that a commercial extract which they examined contained, after purification, an aminohexose similar to glucosamine, and the amino acids, lysine, arginine, glycine, leucine, hydroxyproline and aspartic acid. The aminohexose yielded pyrrol groups upon condensation with acetylacetone and ammonia, and treatment with alkali (Journ. Biol. Chem., 1935, 109, 489).

More recently Karrer has analyzed a highly purified preparation. He reports that it is acetone-insoluble and contains tryrosine and arginine, but is free from phenylalanine, proline, hydroxyproline, glycine, tryptophane and histidine.

The liver possibly contains at least one other hemopoietic substance besides that effective in pernicious anemia. Wills produced a macrocytic hyperchromic anemia in monkeys by means of dietary defects which failed to respond to highly purified liver extracts, but were cured by crude liver preparations or by yeast, marmite, wheat germ or liver, all of which are rich in the vitamin B complex. The nature of this material, though apparently related in some way to the vitamin B complex, is unknown.

1929 by Castle who found that the gastric contents of a normal person during the digestion of meat were curative when fed to a subject of pernicious anemia. Later Castle and his associates showed that pure gastric juice obtained from a normal person by the administration of histamine when incubated with beef-steak produced the curative material. The active principle was not produced when beef was incubated with gastric juice of a patient with pernicious anemia. The production of the anti-anemic principle is not due to the action of hydrochloric acid, pepsin, rennin or lipase but to the presence of an enzyme-like substance which acts at a pH of 7 (the optimal pH for the action of pepsin is 1.6). Just before this, Sturgis and Isaacs found that gastric tissue contains the material necessary for the formation of the anti-anemic factor, it being, like liver itself, effective in

acts upon a material in certain articles of diet to produce the specific principle. Castle refers to the gastric material as the "intrinsic" factor and to the dietary precursor as the "extrinsic" factor.

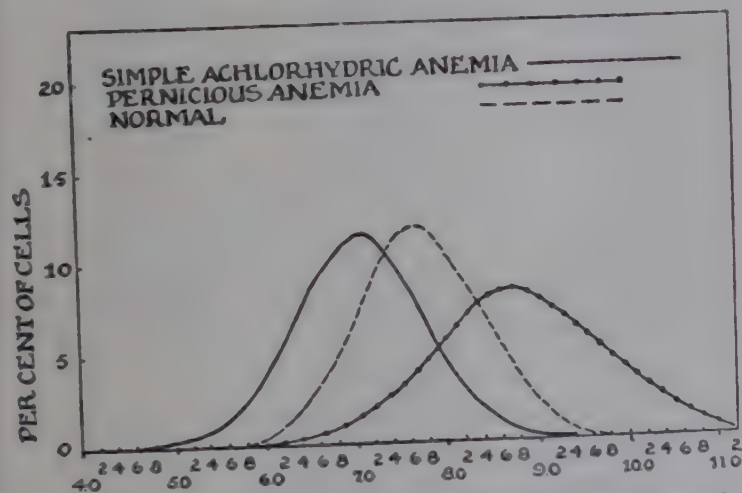


FIG. 19. Red-cell-diameter distribution curves in simple achlorhydric anemia and in pernicious anemia compared with the normal (after Haden; see also fig. 20).

the treatment of pernicious anemia. Desiccated de-fatted hog stomach is now employed as an alternative to liver or liver extract for oral administration. The gastric factor is less stable than the liver principle, being destroyed by temperatures above 45°C. and by prolonged digestion with pepsin or trypsin. In the hog, the intrinsic factor is produced by the mucosa of the pyloric and cardiac regions of the stomach and the commencement of the duodenum, i.e., regions which secrete an alkaline juice (pyloric, cardiac and Brunner's glands). In the human subject the intrinsic factor, according to Fox and Castle, is formed in the fundus of the stomach; none is found in the pyloric region nor in the duodenal secretions.

Two factors are concerned therefore in the production of the anti-anemic principle. An enzyme-like substance in healthy gastric juice or in the stomach tissue of man and certain animals which

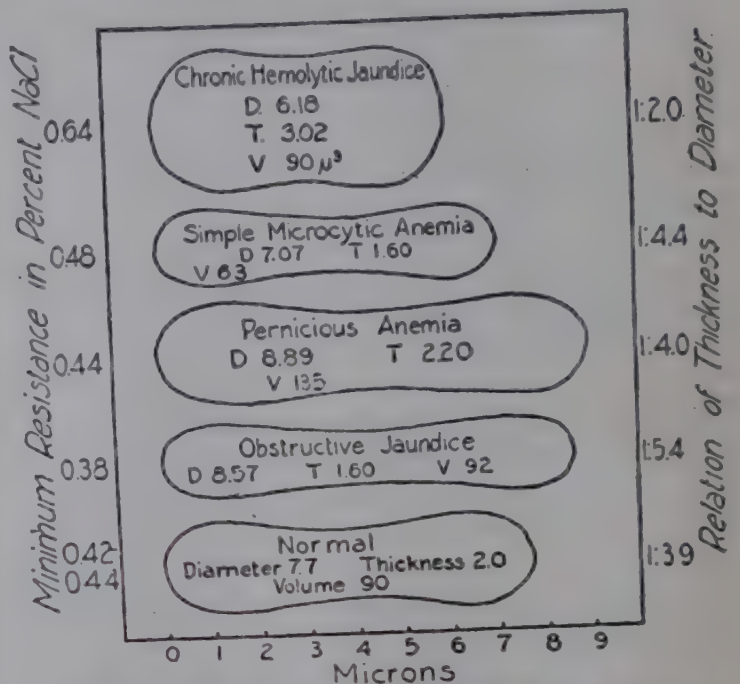


FIG. 20. Red cell diameter, thickness and volume in various clinical conditions compared with the normal (after Haden). D, diameter; T, thickness; V, volume.

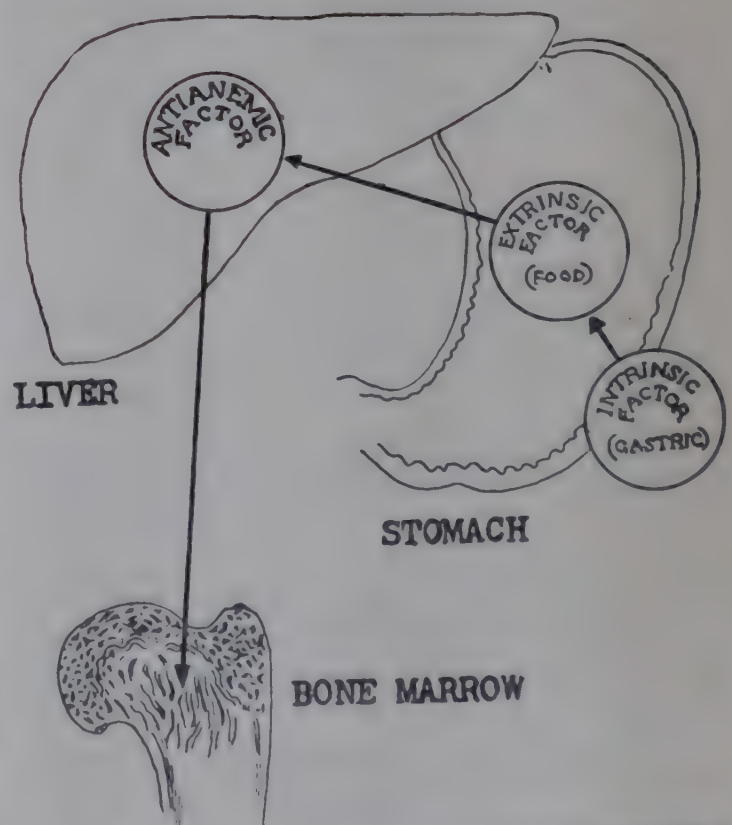


FIG. 21. Diagram to illustrate the factors responsible for normal erythropoiesis.

The theory which fits these facts best and relates them to the cure of pernicious anemia is the following. In health the essential anti-anemic principle is derived from food through the action of the "intrinsic" (gastric) factor upon an "extrinsic" factor contained in the diet. The anti-anemic

principle so formed is stored in the liver and possibly other organs, to be drawn upon for the maintenance of normal activity of the erythropoietic tissue (bone-marrow). Pernicious anemia follows if the essential enzyme is absent from the gastric juice.² The anti-anemic principle can therefore be given pre-formed as in liver or liver extract, or gastric tissue and a well-balanced diet can be given from which the patient manufactures his own supplies (fig. 21).

A characteristic lesion is found in pernicious anemia which readily explains the achlorhydria and the lack of the intrinsic factor. The fundus and body of the stomach show atrophy of the mucosa and extreme thinning of all coats. The gastric glands are almost completely destroyed; the muscular coat is atrophic. The pyloric region, which does not produce the intrinsic factor, is normal. One would be led to expect that total gastrectomy in man would be followed by pernicious anemia, yet this is not the case. Only seldom has such a result been reported. The hypochromic type is more frequently a sequel of gastrectomy. Even removal of the entire stomach from dogs is not followed by pernicious anemia. The reason that pernicious anemia does not follow removal of the entire stomach has received no entirely satisfactory explanation. The most probable reason is that the survival time (1–2 years) following the operation in man (usually for carcinoma) is too short for the development of the disease.

The nature of the "extrinsic" factor

Castle found that when autolyzed yeast was acted upon by normal gastric juice the anti-anemic factor was produced. Autolyzed yeast alone was ineffective. He concluded that the extrinsic factor was either vitamin B₂ or a substance closely related to it. It has been shown, however, by Wills that egg-white and other sources of B₂ when acted upon by normal gastric juice do not yield the anti-anemic principle; therefore, though beef, rice polishings, wheat germ and marmite are rich sources of the extrinsic factor, this is not vitamin B₂.

Though anemia of the pernicious type is most commonly due to the absence of the intrinsic

² The foregoing theory implies, of course, that the gastric defect is the direct cause of the blood condition. Yet, though achlorhydria is present in about 5 per cent of persons, only a small proportion develop pernicious anemia; indeed the hypochromic (p. 63) type of anemia is more likely to result. The probable reason is that in the cases of achlorhydria in which pernicious anemia does not occur, the intrinsic factor is not lacking. Some observations of Castle, who found the intrinsic factor present in cases of achlorhydria without anemia, are in accord with this explanation.

factor, it quite obviously could also result from (a) lack of the extrinsic factor in the diet, (b) failure of the anti-anemic principle after its production in the stomach to be absorbed from the intestine, (c) inability of the liver to store the principle, or (d) failure of the latter to be utilized by the hemopoietic tissues. It appears that any one of these stages in the hemopoietic mechanism may be interfered with and an anemia of the pernicious type result. Thus, in *sprue* (steatorrhea, p. 657) an anemia of this type occurs which is attributed to failure of absorption of the hemopoietic factor. Anemia of the same type occurs in certain other intestinal diseases or when the gastric contents are short-circuited into the colon through a gastrocolic fistula. An anemia is seen in the tropics, chiefly in India, which has been attributed to a lack of the extrinsic factor in the diet. But an anemia closely resembling this tropical variety has been produced in monkeys which, as stated in a footnote on page 64, is cured by a crude liver extract but not by one that is highly purified, suggesting that some instances, at least, of the tropical disease may also be due to the lack of a second hemopoietic substance in liver. In very severe *hepatic disease* a macrocytic anemia may develop which is attributed to a failure in storage of the hematinic principle;³ the *pernicious anemia of pregnancy* is probably due to exhaustion of the principle owing to the heavy drains upon the maternal supplies for fetal hemopoiesis. Lack of hydrochloric acid in the gastric juice and a diet lacking the extrinsic factor may be contributory causes. An anemia with a blood picture identical with that of pernicious anemia has been described which does not respond to treatment with liver extracts. It is due apparently to a defect in the utilization of the anti-anemic principle, for the livers of subjects of the disease contain the latter in adequate amounts. The term *achrestic* (Wilkinson) has been applied to this very rare form.

The response to liver or gastric tissue

The anti-anemic principle acts upon the bone marrow, restoring the blood-forming processes to normal. The maturation of the erythrocytes is hastened, the primitive cells of the marrow—megaloblasts—disappearing to be replaced by cells of later stages of development, e.g., late erythroblasts and normoblasts (see p. 84). This specific

³ It has been reported, however, that in some of these cases at least, the liver contains adequate amounts of the hematinic principle. The cause of the macrocytic anemia in these instances is unexplained.

effect of the active principle has been demonstrated by Sabin who found that the addition of liver extract to the early chick embryo accelerated the division and maturation of the primitive megaloblastic cells of the blood islands. Müller demonstrated a corresponding effect upon the bone marrow of pigeons. When these birds are starved the marrow becomes aplastic but subsequently, when a diet of grain is fed, the marrow becomes hyperplastic and packed with megaloblasts. That is, a state of the marrow comparable with that seen in pernicious anemia is induced. By adding liver to the diet the hyperplastic reaction was inhibited, the megaloblasts disappeared and the marrow assumed a normal appearance. Peabody also found that marrow removed during life from pernicious anemia patients, showed a reduction in the number of megaloblasts and a preponderance of normoblasts as a result of liver feeding.

The first detectable effect of specific treatment in pernicious anemia is a rise in the reticulocytes. In untreated cases of pernicious anemia these constitute 3 per cent or less of the red cells. In from 3 to 5 days after liver, a potent liver extract, or a gastric preparation has been given, large numbers of reticulocytes appear. The increase reaches its maximum about the fifth day, when the percentage is from 10 to 40 per cent. From then on the reticulocyte population declines, the immature cells having undergone maturation in the blood stream (fig. 22). This is reflected in an increased number of mature erythrocytes. The increase in the number of red cells, other things being equal, is proportional up to a point to the quantity of liver extract administered.⁴ When adequate amounts are given an increase to about the normal level occurs within 60 days. The lower the red cell count before treatment, the greater is the reticulocyte response to specific therapy. This fact is interpreted as indicating that in the more severe forms of the disease, megaloblasts constitute a large percentage of the marrow population; the anti-anemic principle hastens the development of these primitive forms to reticulocytes which are then promptly expelled into the circulation. When, on the other hand, the anemia is less severe the percentage of later forms, e.g., normoblasts in the marrow is greater and the stimulus to maturation exerted by the liver principle carries them to the adult stage. A larger proportion of mature eryth-

rocytes is therefore discharged into the circulation. In cases in which the red cell count is 3 million or over only a slight rise in the reticulocytes occurs, the rise in the red cell count being then due almost entirely to an increase in the number of mature cells.

The rise in the hemoglobin concentration of the blood lags behind the multiplication of the red cells so the color index returns to normal within a short time. If the stimulus to erythropoiesis is intense, the hemoglobin cannot be manufactured in sufficient quantities to furnish each cell with its quota of pigment and the color index falls well below the normal value.

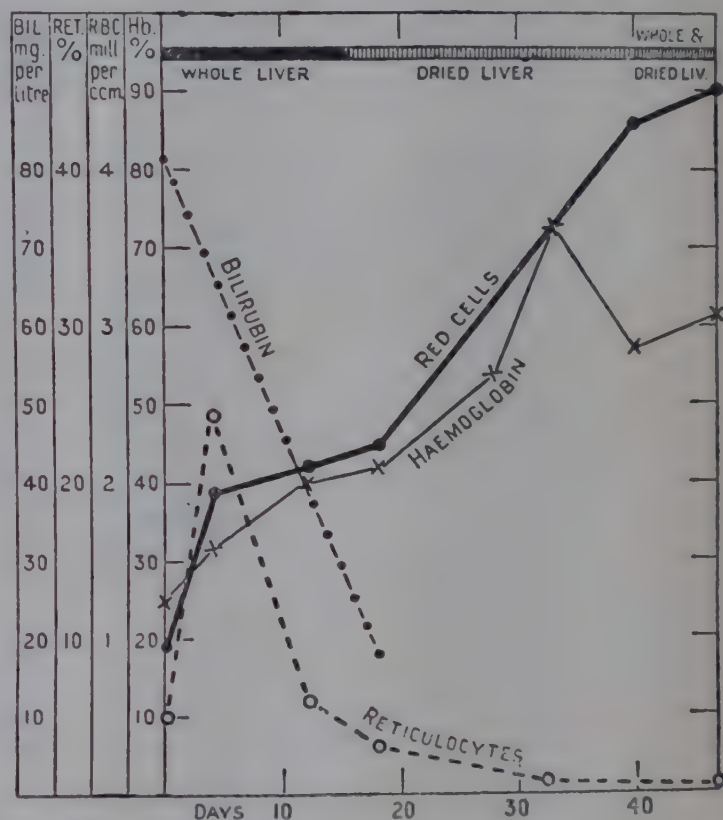


FIG. 22. Showing effect of specific liver therapy upon the reticulocytes, erythrocytes, hemoglobin and plasma bilirubin (after Dyke).

With the improvement in the blood picture the general symptoms of the disease abate, but the secretion of acid gastric juice is very rarely restored. Liver treatment therefore does not remove the primary cause of the disease and its administration must be persisted in for the rest of the patient's life. The maintenance dose, is of course, much less than that required originally for the restoration of the normal blood picture. Cord changes which have occurred may be favorably affected if sufficient liver or liver extract is administered (p. 868). The nervous lesions are due, mainly at any rate, to a lack of the liver principle and not simply secondary to the anemia. Therefore, an amount of the liver principle which

⁴ The reticulocyte response of a pernicious anemia patient is usually employed in assaying the potency of liver preparations. No satisfactory animal assay method has been found.

TABLE 10
Summarizing chief hematological features of various types of anemia (see also figs. 19 and 20)

ANEMIA	ERYTHROCYTES	RETICULOCYTES	LEUCOCYTES	PLATELETS	BLOOD INDICES			FRAGILITY OF RED-CELLS	PLASMA BILIRUBIN AND PIGMENT EXCRETION
					Color	Volume	Saturation		
Hypochromic types due to iron deficiency	Moderately reduced Microcytes Poikilocytes	Normal or slightly increased			Marked reduction	Reduced	Marked reduction	Normal	Normal
Pernicious types	Greatly reduced Macrocytes Megaloblasts and normoblasts Poikilocytes	3 to 4 per cent	Reduced; with a shift to the right (p. 113) Relative lymphocytosis Leucocytosis in anemia of gastric carcinoma	Reduced	Raised	Raised	Raised	Reduced	Increased
Aplastic	Greatly reduced Primitive forms absent indicating a great reduction or a complete absence of the regenerating power of the marrow	Reduced or absent	Reduced Relative lymphocytosis Normal or reduced	Reduced	Normal or slightly reduced	Normal	Normal	Normal	Normal
Post-hemorrhagic: Acute	Reduced to variable degree Normoblasts Poikilocytes	3 to 10 per cent or so	Neutrophilic leucocytosis	Increased	Normal or moderately reduced	Normal or moderately reduced	Normal or moderately reduced	Normal	Normal
Chronic	Reduced Normoblasts Poikilocytes	Slight increase	Normal or slight reduction		Reduced	Reduced	Reduced	Normal	Normal
Acholic (hemolytic) jaundice	Reduced Normoblasts Poikilocytes Microcytes and polychromasia	5 to 60 per cent	Normal or moderate increase		Normal	Normal	Normal or raised	Greatly increased	Increased

In acholic jaundice it is only the diameter of the cell that is reduced; its thickness is increased so that the volume is about normal.

alleviates the anemia is not necessarily sufficient to arrest the neurological condition.

Macrocytic (hypochromic or hyperchromic) anemias with normoblastic bone marrow

Macrocytic anemias showing a resemblance to Addisonian anemia, in so far as the blood picture is concerned, occur in various diseases, e.g., gastric carcinoma, syphilis, hepatic cirrhosis, etc. But the bone marrow is of the normoblastic type. Since they are not due to deficiency of the anti-anemic principle, they do not respond to the administration of liver extract or of gastric tissue.

IDIOPATHIC APLASTIC ANEMIA

This is a comparatively rare type of anemia in which there is a rapidly progressive reduction in all the blood cells—erythrocytes, leucocytes and platelets. There is little or no evidence of blood regeneration, reticulocytes are very scarce and nucleated forms are usually absent. The red cell count may reach an extraordinarily low figure—213,000 per cubic millimeter in a case reported by Ehrlich. Granulocytes and platelets may entirely disappear. The marrow is hypoplastic or aplastic; there is a great reduction in its cellular elements and almost complete absence of hemopoietic activity. The lymphocytopenia which also occurs, but

is less marked than the reduction in granulocytes, suggests that the entire hemopoietic system is affected. The causes of the bone marrow hypoplasia have been mentioned (p. 62).

A number of cases have been reported recently (Thompson, Richter and Edsall; Anderson) in which the typical blood picture of aplastic anemia was associated with a normal or even a hyperplastic marrow. In these, to which the term "pseudo-aplastic anemia" might be applied, there would appear to be some interference with the maturation and delivery of the cells into the blood stream rather than to absolute suppression of marrow function.

It is only upon pernicious anemia or macrocytic anemias of the pernicious anemia type with a megaloblastic bone marrow that liver therapy has any specific effect. Other macrocytic types (with a normoblastic type of marrow), the microcytic anemias and aplastic anemia fail to respond to the administration of liver extract or to gastric tissue. In post-hemorrhagic anemia and certain other secondary anemias *whole liver* is of value, not from any specific action but simply because it furnishes iron and protein of high quality. The principal features of the blood picture in several types of anemia are summarized in table 10.

CHAPTER X

THE WHITE BLOOD CORPUSCLES OR LEUCOCYTES—THE PLATELETS

CLASSIFICATION AND MORPHOLOGY

The white blood cell differs from the erythrocyte in that it contains no hemoglobin, but has a well formed nucleus. The majority of the white cells are also considerably larger than the erythrocytes, measuring from 8 to 15 microns in diameter, the size depending upon the particular variety. They are much less numerous than the erythrocytes; in the adult they number from 5 to 9 thousand per cubic millimeter of blood. In infancy they are twice as numerous and throughout childhood the count is higher than in the adult. When a film of adult blood is examined under the microscope the white cells appear very sparsely scattered here and there among the crowds of colored corpuscles which outnumber them more than 600 to 1.

On a basis of morphological differences the colorless corpuscles are divided first into two main groups: (I) *Cells with a single nucleus and a clear nongranular cytoplasm*—the lymphocytes and the monocytes; (II) *cells having a lobed or incompletely partitioned nucleus, and a cytoplasm containing fine chromophil granules*—the *granulocytes*. Each of these two main classes are divided further into subgroups on a basis of differences in structure or staining properties¹ (see frontispiece).

I. THE NON-GRANULAR LEUCOCYTES— AGRANULOCYTES

These are of three varieties: (1) *Small lymphocyte*, (2) *large lymphocyte*, (3) *monocyte*. Though these forms show no granules in the protoplasm under the ordinary methods of staining, granulation may be demonstrated after staining with azure-blue. The lymphocytes contain a few coarse azurophil granules; those of the monocytes are fine and very numerous.

(1) **THE SMALL LYMPHOCYTES.** These are slightly larger than the red cells—about 8 microns in diameter. The nucleus is relatively large, slightly indented and stains more deeply with basic dyes than the surrounding narrow rim of cyto-

plasm which separates it from the boundary of the cell. The small lymphocytes originate in lymphoid tissue and are found in large numbers in the lymph nodes and spleen. They constitute in the adult from 20 to 25 per cent of the total number of white cells in blood and are the commonest cells found in lymph. In childhood lymphoid tissue is much more abundant than in adult life and the lymphocytes are more numerous. They amount to from 50 per cent or more of the leucocytes in early childhood and to about 35 per cent at the age of ten years.

(2) **LARGE LYMPHOCYTES.** These resemble the preceding in general appearance but are considerably larger, being 12 or more microns in diameter. The cytoplasm forms a wider zone about the nucleus, which is oval or kidney shaped. These cells are found in insignificant numbers in adult blood but are more plentiful in the blood of young children. They are practically confined under physiological conditions to the lymphoid tissue, but even here they are greatly outnumbered by the small lymphocytes. They are considered by many as a younger form of the small lymphocyte.

(3) **THE MONOCYTES** are from 10 to 15 microns in diameter. They possess a relatively larger amount of cytoplasm. The nucleus has a deep indentation on one side, which gives it a kidney or saddle-bag shape. On the supposition that this cell represented a stage in the development of the polymorphonuclear leucocyte, it was called the "transitional leucocyte" by Ehrlich. This view has since been shown to be wrong, for the monocyte bears a relationship to the lymphocytes rather than to the polymorphonuclears. It has been mentioned that the monocyte contains, like the lymphocytes, azurophil granules in the cytoplasm. The monocytes are actively motile and phagocytic, and are considered by most observers to be derived from fixed histiocytes (p. 80). Such an origin would class them as circulating elements of the reticulo-endothelial system. According to Maximow, however, they arise from lymphocytes. They constitute from 5 to 6 per cent of the white cells.

Small numbers (0.2 per cent) of a slightly different type of monocyte are also found in blood. Its nucleus instead of being kidney-shaped is round or oval. It

¹ The term leucocyte is employed by most authors to denote all the white cells, and this from the simple meaning of the word seems logical. Some, however, confine the term to the granulocytes. The first of these usages will be followed in this text.

was previously known as the large mononuclear leucocyte, but it is probably simply a younger form of the preceding variety.

II. THE GRANULOCYTES

These are divided into three groups according to the staining reactions of their granules. One type—the *eosinophilic*—stains with acid dyes, e.g., eosin; another—the *basophilic*—stains with basic dyes, e.g., methylene blue; and the third type—the *neutrophilic*—with neutral dyes, i.e., mixtures of acid and basic dyes. These staining reactions apply to human leucocytes, but such distinctions cannot always be made in other animal species. The nucleus of a granulocyte is composed of two or more lobes connected together by strands of chromatin.

(1) The **EOSINOPHILS** are not numerous; they amount to no more than 3 or 4 per cent of the total white cell count. The granules which are oval and much coarser than those in the other two varieties are stained a bright red with eosin. The cell is also slightly larger and the nucleus usually bilobed. In certain pathological conditions which will be mentioned later they may form a much larger percentage of the leucocyte population.

(2) The **BASOPHILS** are present to the extent of only 0.5 per cent or less. Their granules stain deeply with methylene blue. Their significance is not known. They have been considered by some observers to be degenerated neutrophils, but there appears to be little doubt that they are a distinct type and like the other granulocytes a product of the bone-marrow. Support is lent to the latter view by the fact that they are increased in conditions associated with excessive marrow activity, e.g., chronic myelocytic leukaemia and polycythemia vera. They are also increased in chronic inflammation of the accessory nasal sinuses.

(3) The **NEUTROPHILS** are by far the most numerous, constituting from 65 to 70 per cent or more of the total number of white cells. Their granules are quite small and are stained a violet tint with neutral dyes. As will be seen presently the neutrophils are actively ameboid in character, i.e., they are capable of locomotion and ingest foreign particulate matter. They are about 10 or 12 microns in diameter.

The Arneth count or index

It was pointed out by Arneth that the number of lobes in any neutrophil depends upon the cell's age, the older cells having the larger number. A five-lobed nucleus for instance indicates a stage in the life of a cell

just preceding its final dissolution; an unlobed but deeply indented nucleus, a very young cell. Five stages in the life history of the polymorphonuclear leucocyte are therefore distinguished corresponding to the number of lobes developed in the nucleus. A count of the nuclear partitions in the cells of a blood film will give the proportion of cells of different relative ages. In figure 23, stage I shows a nucleus with a single lobe. Constriction of the nucleus can be seen but the nuclear substance is continuous from one part to the other. In stage II the nucleus is partitioned into two parts which are connected only by chromatin threads. In the next stage 3 lobes are seen and so on to the last or senile stage in which the nucleus has 5 or more lobes. These latter are large edematous non-motile cells with non-staining granules. In some conditions, e.g., acute septic infections and pernicious anemia, very large cells (up to 20μ) with a great number of nuclei are seen. These are known as *macropolycytes*.

The Arneth index is determined by counting the number of nuclear lobes in each of 100 neutrophils. The cells in the different stages are expressed as percentages of the total. The count under the ordinary conditions of health is as follows:

	Percentage of leucocytes
Stage I.....	5
Stage II.....	30
Stage III.....	45
Stage IV.....	18
Stage V.....	2

In certain diseases the youngest cells (Stage I) are much more numerous and may constitute 50 per cent of the total. There may be an entire absence of cells in the later stages (IV and V). An increase in the percentage of cells of the earlier stages is spoken of as a "shift to the left." It is seen in conditions which stimulate the bone marrow to a greater production of white cells, e.g., pyogenic infections. It is also seen in tuberculosis and after exposure to the X-rays and after the injection of thyroid extract. In children a shift to the left occurs much more readily than in adults. In pernicious anemia the percentages of the older cells increase—"shift to the right"—and in some cases, as mentioned above, macropolycytes appear. Except in the case of the senile non-motile cells a relationship between the phagocytic activity of a particular cell and its age has not been demonstrated.

The *Schilling index* employs a simpler classification of the neutrophils. Four stages are recognized (a) the myelocyte which shows a single spherical nucleus; (b) young metamyelocyte with a slight indentation of the nucleus; (c) older metamyelocytes with the process of lobulation definitely indicated; this is known as the band cell of Schilling or "Staff" cell and corresponds to the first stage of Arneth; (d) older neutrophils, i.e., the other stages of Arneth. Stages (a) and (b) are not

found normally in the blood. They appear when a pronounced "shift to the left" occurs. (See frontispiece and p. 85.)

The non-motile cells of the last or fifth stage of Arneth appear, periodically in increased numbers—in "showers"—in the blood stream. They are replaced by young cells from the marrow. Like



FIG. 23. Arneth stages (after Cook).

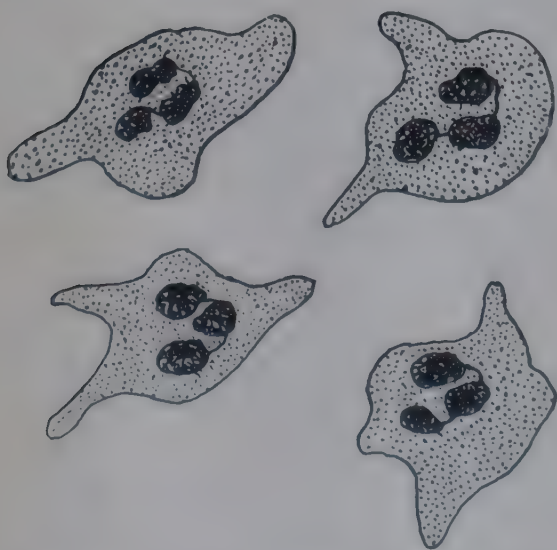


FIG. 24. Sketches of a neutrophil at time intervals of a few seconds.

the red cell the dying neutrophils disintegrate in the circulation or are disposed of by the macrophages of the spleen or the tissues. The life span of the neutrophils has been variously estimated. By some it is believed to be no more than about 3 days and by others no more than a few hours. Ponder, however, puts it at 21 days. He induced a leucocytosis and shift to the left in the Arneth stages by the injection of thyroid extract and fol-

lowed the blood picture until the polynuclear count returned to normal. Since the rise in the count is due to the discharge of young cells (Stage I) from the marrow, when the count again showed the normal percentage of cells of State V it was assumed that the discharged cells had reached the end of their life-span. At any rate the average life of the neutrophils is apparently much shorter than that of the red cell (p. 57).

THE FUNCTIONS OF THE LEUCOCYTES

The neutrophilic polymorphonuclear leucocytes as well as the monocytes and other reticulo-endothelial elements constitute probably the most important elements which the body possesses for its defense against invading microorganisms. Their power to attack bacteria depends upon their motility and a proclivity for the ingestion of solid particles. The latter action which was first demonstrated by Metchnikoff is termed *phagocytosis* (phago—I eat). These two varieties of white blood cell are free lances among the body cells; they wander from place to place through the tissues and practically no part of the body is barred to them. They insinuate a process (*pseudopodium*), improvised at the moment from their cell protoplasm, through one of the joints in the endothelium of the capillary wall. Then by causing the semi-fluid substance of the cell-body to stream into the protoplasmic projection, they pass out of the blood vessels at will. By this action of *diapedesis*,² as it is called, myriads of white corpuscles may pass out of the vessels in a remarkably short time. Reaching a point where the bacteria have entered the body they surround the threatened area and proceed to destroy the invaders. If, for instance, an actively inflamed region should be examined under the microscope, masses of neutrophils would be seen, and many of these would be observed to hold bacteria imprisoned within their bodies. As many as 15 or 20 organisms may be seen at times within a single cell. It has been shown that the germs are ingested alive and remain so for a time within the leucocyte.

When a tissue such as the mesentery or web of a frog, in which the capillaries are clearly visible, is examined in the living state a short time after a culture of bacteria has been injected into it, the small vessels leading to the site of inoculation are found swarming

² The term diapedesis, literally a "leaping through," is sometimes applied to the passage of red cells through an unbroken capillary wall, but the term is scarcely appropriate for a passive process of this nature.

with neutrophils. In the tissues round about, the ameboid cells are seen moving somewhat ponderously hither and thither to engulf the offending bacteria. When the latter are intensely virulent in nature this normal leucocyte reaction may be seriously depressed. The monocytes, though much less numerous, also join in the general attack and show their phagocytic propensities to a marked degree. After the first flooding of the tissues with neutrophils and monocytes, numbers of the latter come to rest and together with other reticulo-endothelial elements of the tissues undergo transformation and aid in isolating the infected area from the neighboring healthy tissues. Until this is accomplished the danger of the infection becoming more wide-spread always exists. In their struggle against bacteria, equipped as these are with powerful toxins, many of the white cells are killed. These collect within the center of the area together with exuded plasma, liquefied tissue cells and a few red cells that have escaped through the injured walls of the capillaries. This material constitutes pus, and the so-called pus-cells are dead leucocytes. The circumscribing wall and its semi-fluid contents constitute an abscess. By the action of the phagocytes, aided by a protein digesting ferment (protease) which they elaborate, the overlying structures whether connective tissue, mucosa or skin are in part removed piecemeal. In this way a communication with the exterior is effected and the contents of the cavity are discharged.

Not only bacteria but practically any foreign material, whether a rose-thorn or a catgut suture is attacked and removed if possible, or loosened by the neutrophils aided by the monocytes and other phagocytic cells of the tissues. The removal of dead tissue or of blood clot or the separation of necrotic from living structures is accomplished in the same way. Devitalized bone though not removed in its entirety, unless it be of very small size is nevertheless eroded and separated from the living tissue by the leucocytes. The disappearance of effete organs such as the tail and gills of the metamorphosing tad-pole or the creeping muscles of insect larvae, as these develop to the mature form, is effected by similar phagocytic cells. The application of heat to a part also attracts leucocytes in large numbers to the capillaries from which they immediately commence to migrate.

The activity of the leucocytes is best studied by the method of Clarke, in which a transparent chamber is inserted into the tissues, e.g., the rabbit's ear. After a time fine vessels grow into the chamber through openings in its sides which may be examined under the microscope. Another very simple method is that of *supravital staining*. A thin film of a non-toxic (supravital) dye, e.g., neutral red, azure, brilliant cresyl blue, is laid upon a glass slide and allowed to dry; a film of blood is laid over this and covered with an ordinary cover glass which is then sealed with vaseline around the edges. The preparation is kept warm and examined under the microscope, the cells remaining alive

and active. The neutrophils seen in such preparations are not round as in fixed smears, but are continually changing their shape. Pseudopodia are in constant movement and the granules can be seen streaming through the cytoplasm with each movement of the cell. The rate of progression of the neutrophil is from 30 to 35 microns per minute at body temperature (fig. 24).

Oxidase reaction. When granulocytes are subjected to the following technique brownish black granules appear in the cytoplasm. Equal parts of a 2 per cent solution of beta-naphthol sodium and a 1 per cent solution of dimethyl-paraphenylene-diamine hydrochloride are mixed, and the mixture filtered. An air-dried blood film is treated with the filtrate. Lymphocytes or monocytes do not give the reaction, which depends upon the presence of specific granules. At the earliest stage in the development of the granulocyte (stage of the myeloblast, p. 84) the reaction is also negative, is ill defined in the next older stage (myelocyte A), but well marked in the more mature forms.

The functions of the other varieties of granulocytes—the eosinophils and basophils—are unknown. The eosinophils are not markedly motile and only slightly phagocytic. Also little is known of the functions of the lymphocytes. A great migration of lymphocytes characterizes certain chronic types of inflammation. By being transformed into fixed connective tissue elements (fibroblasts) they are thought to aid in repair processes. They are not ameboid, that is, they do not progress by the protrusion of pseudopodia. But they are capable of a certain slow progression, as a result of spasmodic movements of the cell-nucleus. The lymphocytes have little phagocytic power and from all accounts possess no proteolytic ferment. They are constantly being shed from the mucous surfaces of the body in enormous numbers, and it has been suggested that they furnish antibodies or in some way serve to adsorb or inactivate toxins, and so contribute toward the body's defenses.

The work of Murphy and others suggests that the small lymphocytes are important elements in the resistance of animals to tuberculosis and to cancer. Tumor tissue or even healthy tissue when transplanted from one animal to another is followed by a great increase in the lymphocytes of the blood and in the tissues in the neighborhood of the graft. Hard X-rays have a selectively destructive action upon lymphoid tissue, and when animals were exposed to the rays the lymphocytic reaction to the grafted cells was suppressed; the animal's susceptibility to the tumor growth was increased. Single small doses of soft X-rays, however, have a stimulating effect upon lymphoid tissue and the production of lymphocytes; animals exposed to these rays showed a marked increase in the

number of lymphocytes in the region of the growth (round-cell infiltration) and their resistance to the graft was increased. Dry heat caused a similar stimulating effect and a corresponding rise in resistance. These blood-cells may also be increased 100 per cent by the injection of foreign protein. The susceptibility of animals to experimental tuberculosis was also shown to be reduced by measures which stimulated lymphocyte reactions.

Trophones. Carrel found that though epithelial cells and fibroblasts could be cultured outside the body in embryonic juice, for the continued growth of these cells in adult plasma the presence of lymphocytes was essential. The lymphocytes elaborate substances from nitrogen compounds (proteins) of the serum upon which the growing cells feed. These nutritive materials or *trophones*, as Carrel calls them, are also produced by the leucocytes in vivo and must constitute an important factor in tissue repair and tissue growth.

VARIATIONS IN THE NUMBER OF LEUCOCYTES IN THE BLOOD STREAM

LEUCOCYTOSIS

In the event of some damage to the tissues which calls forth a leucocytic response, not only is there a migration of leucocytes from the blood to the site of injury, but also a discharge of these cells from the marrow and an increase of their number in the general circulation. Instead of the normal count of seven or eight thousand per cubic millimeters the colorless cells may number 20 to 30 thousand within a short time. *Leucocytosis* is the term used to designate an increase in the total number of white cells. All varieties of the white cells do not necessarily share in the increase. In one instance it may be the neutrophils, in another the lymphocytes or the eosinophils that are increased, and it is the presence in abnormal numbers of one or other of these which then gives the high total leucocyte count. It is often of great diagnostic value to know which type of cell is responsible for the leucocytosis, and in order to determine this a so-called *differential count* of the cells is made. That is, the numbers of the different types in a stained smear of blood are counted and their percentages of the total count are determined. Also, changes in the proportions of the different white cell types may occur though their total number be normal. Such alterations can be revealed only by a differential count. The following example is given in illustration; the lymphocytes and monocytes are relatively increased; the neutrophils and eosinophils reduced.

Total white cells per cubic millimeter.....	75
Lymphocytes, per cent.....	
Monocytes, per cent.....	
Neutrophils, per cent.....	
Eosinophils, per cent.....	

Very commonly an increase in the neutrophils is entirely responsible for the leucocytosis. On account the latter term is used frequently somewhat loosely to imply an increase in count caused by the neutrophilic elements alone. *Neutrophilia* is a more precise term that is coming into use for the latter condition. *Lymphocytosis* and *eosinophilia* are the respective terms employed to designate increase in the other elements.

Acute infections by the pus-forming organisms, staphylococcus, streptococcus, etc., are the most potent causes of a neutrophilic increase. On account the examination of the white cells furnishes a valuable diagnostic sign for the detection of hidden inflammatory conditions, e.g., appendicitis, empyema, etc. A neutrophilic leucocytosis occurs also in pneumonia, whooping cough, scarlet fever, and some other infectious fevers. The nucleated count shows an increase in the young stages at the expense of the older (p. 72).

Chemotaxis is the term applied to the unknown "force" which draws the white cells from their storage houses into the blood stream and from here to the point of injury in the tissues. It was formerly thought that the chemical properties of the bacterial toxin were responsible for this effect, but it has since been shown that nucleic acid and its derivatives (guanine, adenine, adenosine, etc.) are the specific stimulants. Injections of these substances cause a rapid rise in the leucocyte count. Toxins or other injurious agents act probably indirectly by liberating nucleic acid from the tissue cells as well as from injured leucocytes themselves. It has been suggested that the actual force which attracts the cells from the vessels to the tissue focus may have changes in surface tension of the blood cell membrane as its basis, for during the early stages of the inflammatory reaction the leucocytes in the small vessels near the injured site appear "sticky." They collect and cling to the walls of the vessels and are thus separated from the red cells which occupy the axis of the stream. Experiments, however, upon unicellular organisms such as the amoeba to which the white cell bears a strong resemblance have failed to show that the spontaneous movements are surface tension phenomena. It must be admitted that the chemotactic effect still remains a problem to be solved. It has been suggested that the attractive force is electrical rather than chemical in nature, a potential difference being set up between the injured (relatively negative) and

thy tissue, the leucocytes exhibiting the phenomenon of *galvanotropism*. Menken has obtained a crystalline nitrogenous material from inflamed tissues which he states causes increased capillary permeability and the migration of leucocytes through the endothelial wall. He calls this substance *leukotaxine*. On the other hand the expulsion of the crowds of leucocytes from the bone marrow is more probably a vaso-motor action, involving the communication with the general circulation of capillary sinuses filled with cells. There is evidence that capillary sinuses loaded with cells and previously closed from the general circulation are suddenly opened to allow their contents to be swept into the blood stream. This is indicated by the fact, among others, that even the intravenous injection into a rabbit of 1 cc. of saline causes about 300,000,000 mature neutrophils to enter the circulation within an hour.

Physiological leucocytoses. It had formerly been thought that an increase in the neutrophils occurred during digestion—*digestive leucocytosis*—but it seems that this was a misconception. These cells show spontaneous rhythmical variations in their numbers, the total white cell count reaching its maximum of about 10,000 to 8000 in the afternoon, and its minimum, 5000 to 6000 in the early morning. These variations occur quite independently of meals. Leucocytosis also occurs during pregnancy, parturition and menstruation, after muscular exercise and after adrenaline administration, or in states such as fear, pain, anoxia, etc., which cause the liberation of adrenaline from the adrenal gland. In infants and young children the leucocyte count is considerably higher than in adults; the count is also less constant in infancy, varying without apparent cause by two thousand or more per cubic millimeter.

Eosinophilia, or increase in the number of circulating eosinophils, occurs in several conditions, notably allergic states, e.g., certain skin diseases, asthma and anaphylactic shock, and in infections by various animal parasites, e.g., *hook-worm (ankylostoma duodenale)* disease, in which the eosinophils may be 30 per cent of the total white cell count, and in *trichiniasis*. In the latter infection there is a general leucocytosis, with the eosinophils running as high as 50 per cent or more per cu. mm. Infections with hydatids, ascaris and other worms also cause eosinophilia to a greater or less degree. The significance of this association of eosinophilia with parasitic infection is unknown. During the acute stage of pyogenic infections the eosinophils are reduced in number (*eosinopenia*); in the convalescent stage they are increased.

Lymphocytosis. The neutrophils are not stimulated by tuberculous, malarial, or syphilitic infection. In the active stage of such conditions either an absolute or relative increase in the number of circulating lymphocytes is the rule. In other chronic inflammatory states and in infections with the colon or diphtheria bacillus also, it is the lymphocytes rather than the neutrophils that are increased in number. They indicate in general

an inflammatory condition that is undergoing repair is being held in check, or at the most is making slow progress. Lymphocytosis, therefore occurs as an aftermath of acute infections. The neutrophils on the other hand represent the "shock troops" and their presence indicates that a more active campaign is being waged. In young children a relative lymphocytosis is the rule.

Monocytosis occurs in glandular fever, a condition associated with a general enlargement of the lymph glands. The monocyte count may be 15,000 or 20,000 per cubic millimeter. The monocytes are also increased in pulmonary tuberculosis. According to Cunningham a decline in the lymphocyte count and an increase in the monocytes in this condition indicates that the process is being arrested. Monocytosis also occurs in malaria and in syphilis.

The leucocytic responses in the conditions considered in the foregoing paragraphs are "purposeful." That is, they are normal protective reactions. In the blood disease known as *leukemia*, however, an enormous increase in the number of leucocytes is a primary feature and essentially pathological. The white cell count may be 500,000 or more per cubic millimeter. It is a disease that affects the maturation and multiplication of the white cells with the appearance of abnormal forms in the blood stream (p. 85).

LEUCOPENIA

Leucopenia means a reduction in the number of circulating leucocytes. It is seen in certain diseases, notably typhoid fever, and may be induced experimentally by injections of the toxin of the typhoid bacillus—or emulsions of the dead organisms. In some cases in which the white cells are reduced in number in the blood, the reduction is due to their attraction to some solid organ such as the lung or spleen. This has been shown by taking blood counts from various regions. In other words leucopenia may be due to a redistribution of leucocytes in the body, rather than to an actual reduction in their number. A temporary fall in the leucocyte count may precede a leucocytosis. Certain poisons, e.g., benzol, cause leucopenia by depressing the activity of the bone marrow (see also p. 69).

Granulocytopenia, agranulocytosis, etc. *Granulocytopenia* is the term applied to an abnormally low leucocyte count due to the reduction in granulocytes. The lymphocytes and monocytes are but slightly reduced or not at all, so that their proportion of the total count is increased. There may be complete absence of granulocytes when the term *agranulocytosis* is applicable. In

most instances the absence of granulocytes is associated with a severe septic or necrotic condition of the throat. This condition, called *agranulocytic angina*, is fatal in the great majority of cases. The cause of these conditions is unknown but the fault is evidently one of the bone marrow, and is probably induced by some toxic agent. The marrow shows, frequently, an almost complete suppression of granulocyte formation but is normal so far as erythropoiesis is concerned. In animals reduction in the granulocytes is readily induced by the administration of benzol which acts specifically to depress marrow activity and there is a belief that in some cases agranulocytosis is induced by certain benzol derivatives employed for their antipyretic or analgesic properties. The arsenobenzenes, dinitrophenol and, though rarely, sulphanilamide and sulfathiazole have been incriminated. Amidopyrine is a drug which has been most strongly suspected in this connection. In the treatment of these conditions, pentose nucleotide is employed with the object of stimulating the granulopoietic functions of the marrow.

In some cases of agranulocytosis there is also a marked reduction in lymphocytes and bone marrow shows an increase in the number of primitive cells of the granulocyte series (myelocytes and myeloblasts). The maturation of granulocytes is apparently arrested at an early stage, (p. 84). From the analogy between this fault in granulopoiesis and the erythropoietic abnormality seen in pernicious anemia, the condition has been termed *pernicious leucopenia*.

THE BLOOD PLATELETS (THROMBOCYTES)

These are commonly stated to be simply fragments of protoplasm (i.e., non-nucleated) derived from the cytoplasm of the megakaryocytes (p. 85). Their colorless cytoplasm contains two types of granules. Those of one type are arranged in clumps or chains and stain supravitaly with neutral red. The other type are discrete and stain supravitaly with Janus green. The platelets have an average diameter about a third that of a red cell, namely, 2.5 microns, and number from 200,000 to 400,000 per cubic millimeter. They vary considerably in shape. Their best known function is concerned with the mechanism of blood-clotting (p. 88), since they are believed to liberate throm-

bokinase when they disintegrate. The disintegration of the platelets is said to occur more readily in blood drawn during the digestion of a meal of meat.

Variations in the number of platelets occur in the following conditions. They are *increased* after a meal of meat, after hemorrhage, and in certain allergic conditions, in myeloid leukemia and in convalescence from infections.

They are *diminished* in purpura hemorrhagica, aplastic anemia, pernicious anemia, in anaphylaxis and in the acute stage of septic infections.

The number of platelets per cubic millimeter is determined most conveniently by diluting a sample of blood with a fluid composed of sodium citrate 3.8 per cent, formalin 0.2 per cent and brilliant cresyl blue 0.1 per cent, and counting immediately. The proportion of platelets to red cells (normally about 1 to 20) is determined. If the number of red cells per cubic millimeter be known then the corresponding number of platelets is readily calculated.

Besides their well-known rôle in the coagulation of blood (p. 88) the platelets probably serve other functions. They have a pronounced tendency to agglutinate into masses and to form deposits upon any roughened surface or foreign material. Particles of India ink or microorganisms injected into the body become surrounded by a mass of agglutinated platelets. They may therefore aid in the body's defense against infective organisms. It is probable also that they serve to seal leaks in the capillaries by adhering to small defects which may occur from time to time in the delicate endothelial wall. They constitute the first defense against the loss of blood from larger vessels. Collecting around the margins of the vascular wound they help to close it, or at any rate serve to fasten the clot, which subsequently forms, to the vascular wall, and, through their action in inducing retraction and consolidation of the clot, to narrow the opening in the vessel and form a firm plug within its lumen.

CHAPTER XI

THE ORIGIN OF THE BLOOD CELLS

INTRODUCTION

There are two main schools of thought concerning the development of the blood cells in postnatal life. (a) The *unitarian* or *monophyletic* school holds the view that all types of blood cell are derived from a common primitive free cell which they term the "*stem cell*" or *hemocytoblast*. (b) The *dualistic* school believes in the existence of two distinct types of stem cell, one in the bone marrow which gives rise to the myeloid elements—erythrocytes, granulocytes and megakaryocytes, and the other in lymphoid tissue which is responsible solely for the genesis of the lymphocyte. It is not possible to speak unreservedly for either theory though the unitarian view seems to have the balance of evidence in its favor and will be followed in this text. Both schools are agreed, however, that in the early embryo the mesenchyme gives rise to a primitive free cell from which all the blood cells are derived. It is also generally conceded that certain cells of the bone-marrow and lymphoid tissues of the adult (p. 78) are the representatives of the mesenchyme cells of the embryo and to such cells all the blood cells trace their lineage.

The point at issue is, "Do the bone-marrow and lymphoid tissues give rise to two cell types, with their potentialities restricted, the one to the development of myeloid elements, the other to the development of lymphocytes?" Or, "Do both types of tissue give rise to a primitive free cell—the stem cell or hemocytoblast—with potentialities for the production of all types of blood cells, but whose development along one or other line is determined simply by its immediate environment?" The latter is the monophyletic view (Pappenheim, Maximow).

It is not maintained, however, that the individual blood cells arise, under ordinary circumstances, in direct line of development from the stem cells, that is, each blood cell from a hemocytoblast. In health, the blood cells are produced through the multiplication of cells belonging to later stages of hemopoiesis (erythroblasts and myelocytes, p. 83 and p. 85). In other words a single stem cell is the ancestor of many millions of mature blood cells. This type of development, involving the proliferation of cells of later stages

and the production of daughter cells of the same type which then undergo maturation, is called *homoplastic hemopoiesis*.

Under pathological conditions, on the other hand, the stem cells may undergo active proliferation, and produce, directly, immature blood cells (erythroblasts of various ages, myeloblasts and myelocytes). This is termed *heteroplastic hemopoiesis*.

The schemata shown below will enable the reader to follow the description of the blood cell origins which will now be given.

HEMOPOIESIS (BLOOD FORMATION) AT DIFFERENT EMBRYONIC AGES IN THE EARLY EMBRYO

The yolk sac. The first signs of blood and blood vessels appear in the mesenchyme of the wall of the yolk sac, i.e., outside the embryonic area proper. At a very early stage groups of mesenchyme cells in this situation—the *blood islands of Pander*—are first observed to arrange themselves into cords or columns which soon separate into a central and two outer layers.

The outer two enclosing layers form the walls of the primitive blood vessel—*primitive endothelium*. Of the central group some go to form the first blood cells, while the secretion or actual solution of others forms the *plasma* in which the cells are floated. These free floating elements are known as the *primitive blood cells*. After this the mesenchyme loses its power to produce blood cells directly. A few primitive blood cells may arise from the primitive endothelium from time to time but they are few in number and the process is believed to be relatively unimportant in most mammals, and does not persist for long. The further development of the primitive blood cells follows one or other of two courses. (a) Some of the cells—*primary erythroblasts* and *erythrocytes*—acquire hemoglobin and serve as oxygen carriers. These are short lived and soon disappear forever. (b) The rest remain colorless and apparently unchanged from their primitive state; *they are very similar to, if not identical with, the large lymphocyte*. These cells are found in adult bone marrow and lymphoid tissue, and in small numbers in circulating blood. They are termed by Maximow "*hemocytoblasts*" and upon them the monophyletic conception of blood formation in post-embryonic life is based. They are the "*stem cells*" and are, according to the unitarians, potentially capable of producing any of the blood cells in the adult. Though these cells are identical, morphologically, with the primitive blood cells of which they are an older stage, apparently they are functionally

different, for they form *secondary* erythroblasts and erythrocytes (which the primitive cells do not) but never *primary* erythrocytes (see chart, p. 79). They also give rise to megakaryocytes. The latter are enormous cells (40 μ) with multi-lobed nuclei. The primitive endothelium as well as the primitive blood cells gives rise to hemocytoblasts and also to a few histiocytes (p. 80) which show phagocytic proclivities, devouring degenerated red cells. In mammals few granulocytes are formed within the yolk vessels. They arise extravascularly from hemocytoblasts derived from the mesenchyme cells.

IN THE BODY OF THE EMBRYO. While these stages of blood-development are proceeding in the mesenchyme of the yolk-sac, the heart and vessels are developing in the embryonic area. Soon the embryonic and extra-embryonic systems of vessels form communications with one another and the primitive blood-plasma, primary erythrocytes and hemocytoblasts flow into the body of the embryo. The mesenchyme cells of the general connective tissues of the embryo's body also form hemocytoblasts at this time. From these stem cells secondary erythrocytes and later, granulocytes and lymphocytes are produced. Blood formation throughout the general mesenchyme is, however, of short duration. Hemopoiesis soon becomes localized in the liver, spleen, bone marrow and lymph glands. Normally it is only in these situations that the mesenchyme cells exhibit their powers of producing hemocytoblasts; therefore, it is exclusively in these tissues that the hemopoietic function for a time is carried on.

IN LATE EMBRYONIC AND POST-NATAL LIFE

In the later part of pre-natal life of most animals, the liver and spleen (except the lymphoid tissue of the latter) lose the power to produce stem cells and so, no longer serve as blood forming organs. The hemopoietic function from now on resides solely in the bone marrow and lymphoid tissues (p. 82). The marrow is concerned with the production of red cells, granulocytes and platelets; the lymphoid tissue of lymph glands, of the Peyer's patches of the intestine, and of the spleen and thymus form lymphocytes. In certain animals, such as the opossum and frog, the formation of red cells (erythropoiesis) and of granulocytes (granulopoiesis) is continued throughout adult life by the spleen. In the bird though the marrow is the chief organ for blood formation the liver still retains in part its embryonic hemopoietic function.

In late embryonic and post-natal life the mesenchyme gives rise to three main types of cells.

(a) Those which retain their embryonic potencies throughout adult life, being capable of producing hemocytoblasts (stem cells) and so of generating any of all of the blood cells. Some of these, called the

embryonic reticular cells, are situated in the reticulum of the bone-marrow and of the lymphoid tissue. Ordinarily these cells, as stated on page 77, are restricted in their hemopoietic activities, the great majority of the blood cells in conditions of health being formed by the divisions and re-divisions of cells of their own kind (homoplastic hemopoiesis). Cells having similar potencies are also present in the general connective tissues, and in these situations are spoken of as *undifferentiated mesenchyme cells*. Under ordinary circumstances these latter cells do not give rise to stem cells. As the result of some abnormal stimulus, however, their dormant powers inherited from their mesenchyme ancestry may become aroused and they may then give rise to the various types of blood cells. For example, areas resembling marrow tissue may be produced by the experimental stimulation of these undifferentiated cells; the several types of blood cells are formed within such areas. Maximow rendered the kidney of the rabbit necrotic by tying the renal vessels, and thereby induced in this situation hemopoietic activity resembling that which occurs in adult red-marrow. Marrow-like tissue producing erythrocytes and granulocytes may also arise as a result of an abnormal stimulus, in the spleen, liver, adrenals, aorta, lymph nodes and other sites. In certain forms of anemia, especially of infants, the extra-medullary formation of red cells sometimes occurs (in kidney, spleen, liver, etc.) and in leukemia, granulocytes, which normally arise only in the bone marrow, are produced by the spleen.

(b) The second type of cell has retained a certain measure of its embryonic characteristics. These cells are endowed with the remarkable power of altering their form and functions under appropriate stimulation. They are found in the general connective tissues lying among the fibroblasts. They are allied to the connective tissues on the one hand and on the other to certain white cells (monocytes) of the blood and so form a connecting link between the tissues and the circulating cells.

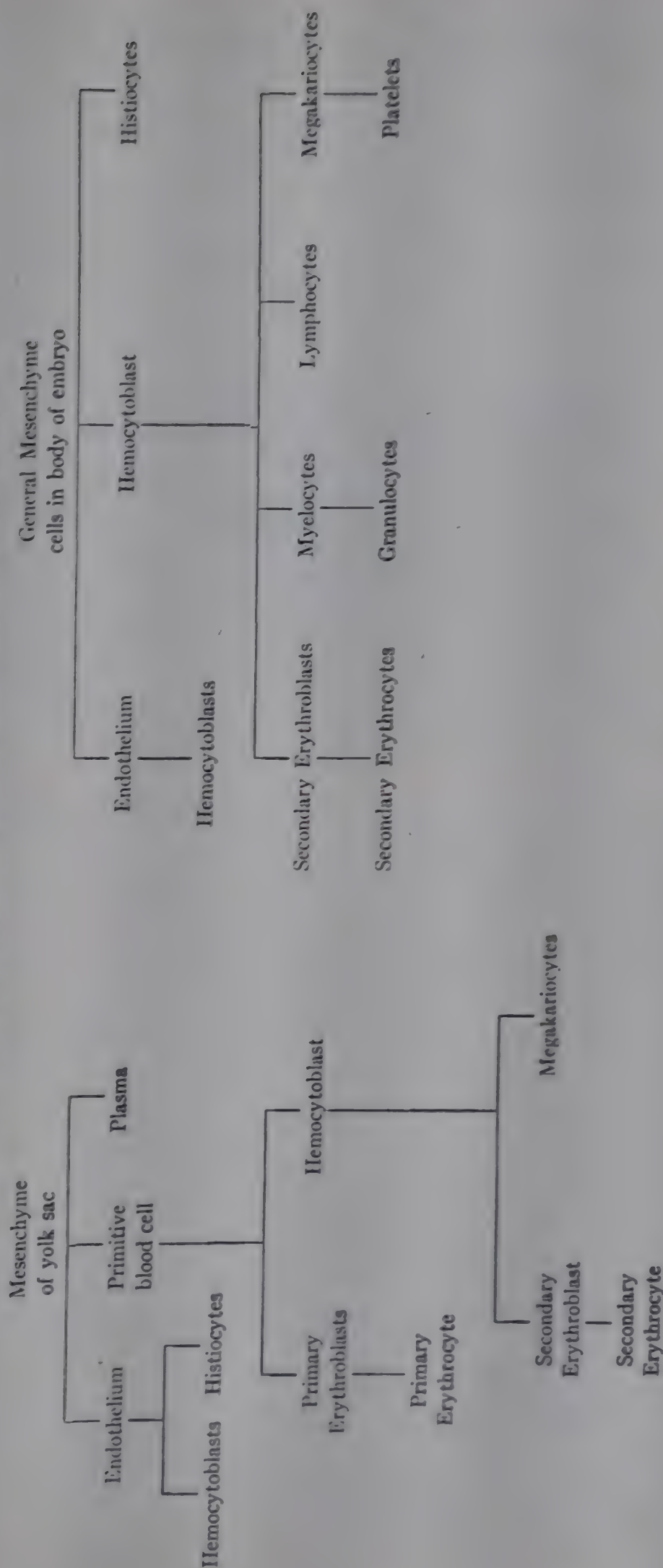
The cells of this group constitute what has been termed by Aschoff the *reticulo-endothelial system* (see below).

(c) In the general connective tissues the great majority of the original mesenchyme cells become transformed into the ordinary and completely differentiated connective tissue elements—the fibroblasts. These, once formed, remain practically unchanged in structure and in function.

THE RETICULO-ENDOTHELIAL SYSTEM

To the cells of this system the general term *histiocyte* has been applied. The term simply means a tissue-cell, and on this account is without descriptive value. But it would be difficult to coin a word that would embrace all the various cell-types of this system, and yet would be sufficiently explicit to distinguish them from some of

Diagram to show the development of the blood cells in the early embryo



the blood cells. *Pyrrol* cells is a term that has been used in the past for a reason that will appear presently. The different types of histiocytes possess one characteristic in common. They are phagocytic for foreign particles of all sorts; and for this reason they were called *macrophages* by Metchnikoff to distinguish them from the much smaller phagocytes of the blood—the neutrophils or *microphages*. In one particular, however, the histiocytes differ from all other cells of the body—neutrophils included. They are stained in the

VARIETIES OF RETICULO-ENDOTHELIAL (R.E.) CELL

The reticulo-endothelial cells or histiocytes may be divided for the convenience of description into two groups—*fixed* and *wandering*. (Cf. chap. p. 81.)

I. Fixed R.E. cells

(1) OF THE COMMON CONNECTIVE TISSUES (TISSUE HISTIOCYTES) and of the loose tissue of the serous membranes, e.g., omentum, pleura, etc. These are also sometimes referred to as “resting wandering cells.”



FIG. 25. Liver from an animal after the intravenous injection of India ink. K, Kupffer cells loaded with ink particles; L, liver cells.

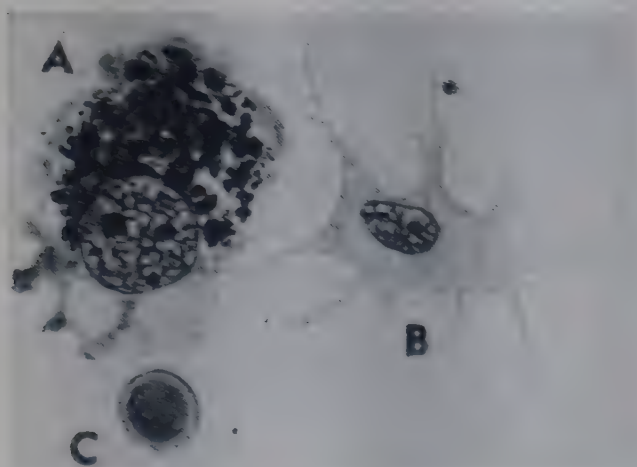


FIG. 26. A, macrophage loaded with particles of India ink; B, macrophage showing processes. C, red cell.

living state by weak solutions of certain colloidal dyes—pyrrol-blue, trypan blue, lithium carmine, etc. The vital or supravital staining reaction is simply a process of ultramicroscopic phagocytosis. That is, the fine ultramicroscopic particles of the dye are taken up from the solution (which is too dilute to stain ordinary cells) and as a result of their accumulation into larger masses in the cytoplasm become visible under the microscope. It is by means of this reaction that the macrophages are able to be detected among the ordinary tissue cells from which it is sometimes otherwise difficult to distinguish them.

Their morphological characteristics are various. Some are round or spindle-shaped, others are squamous, while many have long mobile processes. They lie among the fibroblastic elements and often can be distinguished only with difficulty from the latter except by their special staining reactions. They may at any time as a result of some stimulus, particularly one of an inflammatory nature, become free and wander through the tissues. After the stimulus has been removed they may again come to rest.

(2) OF THE RETICULUM of the spleen, lymph glands, and bone marrow. These are large cells joined to one another by means of long branching processes. They lie among, and are attached to, the fibers of the reticular stroma. They too, given the necessary stimulus, may become detached and actively motile.

(3) FLAT ENDOTHELIAL-LIKE CELLS lining the blood sinuses of the spleen, bone marrow, adrenal cortex and pituitary. This group also includes those most interesting structures—the large flattened stellate cells in the blood sinuses of the liver (Kupffer cells). The latter possess many branching processes and project into the capillary lumen. In many instances they are almost free, being moored to the capillary wall by a delicate strand of protoplasm. At other times they may become quite free to be carried away in the blood stream (fig. 25).

(4) MICROGLIA of the central nervous system.

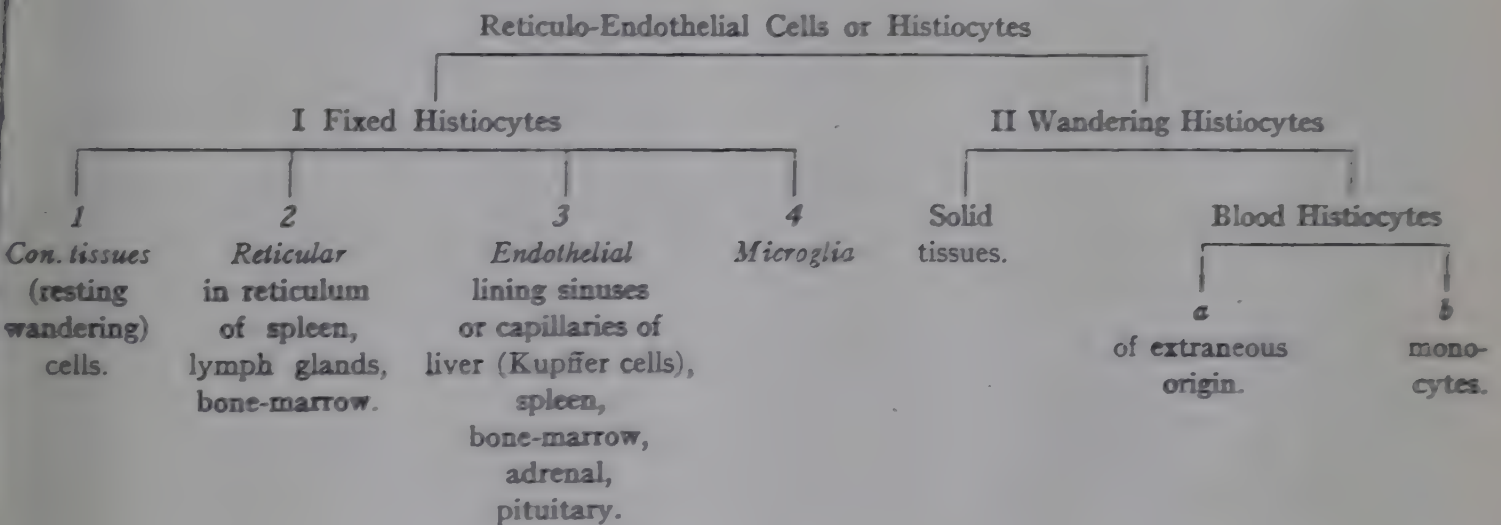
II. Wandering R.E. cells or free histiocytes

(1) **OF THE SOLID TISSUES.** From the foregoing it is seen that many of the fixed histiocytes may upon occasion become actively motile. Large cells of this type are found in the general connective tissues, in the peritoneum, in the splenic pulp and in the lymph glands, bone marrow, etc. (fig. 26). The wandering cells may on the other hand come to rest and become fixed for a long time. On account of the many different forms which these wandering macrophages may assume as a result of an inflammatory stimulus (p. 82) Maximow has named them *polyblasts*.

(2) **OF THE BLOOD.** (a) *Of extraneous origin.* Under certain circumstances as a result of some intense pathological stimulus (e.g., leukemia, bacterial endocarditis), the ordinary tissue macrophages already mentioned may be found in large numbers in the blood stream. They arise chiefly from the spleen and bone-marrow and swarm into the venous system, but rarely

like the fibroblast and has no characters in common with the so-called endothelial cells of the sinuses of the bone marrow, spleen, etc. These are called *littoral* (shore) *cells* by Maximow. They are relics of the primitive endothelium.

From the account of the histiocytes which has been given it is quite evident that phagocytosis is one of their chief functions. In this they constitute one of the most important and powerful means by which the defense of the body is sustained. Their action though similar to that of the neutrophilic leucocytes is less mobile and more localized in character. They, with the aid of the lymphocytes, contribute toward the repair process which follows the acute phase of a tissue injury. The various types are for the most part readily transformable, one into another, the different



reach the arterial side, for, on account of their huge size (30μ) they are strained out by the capillaries of the lung. Large numbers may be obtained from the right heart but few if any from the left.

(b) *Monocytes* (see p. 70). The origin of these normal elements of the blood has been the subject of considerable controversy. According to some, they arise solely from histiocytes, especially of the spleen and bone marrow, and are therefore classed with the reticulo-endothelial system. Lewis has shown that in hanging drop cultures macrophages may be transformed into monocytes, or vice versa. Maximow, on the contrary, believes that the monocytes arise from lymphocytes, stating that in certain situations, e.g., in the spleen, all transitional stages from lymphocyte to monocyte may be seen.

FUNCTIONS OF THE RETICULO-ENDOTHELIAL SYSTEM

The word "endothelial" is not quite appropriate. The cells lining the blood sinuses are not true endothelial cells. The ordinary endothelial cell of the blood vessels is a highly differentiated cell

forms which they assume being determined by local environmental conditions and the nature of the stimulus. Any of the stationary cells may change into wandering histiocytes (macrophages) or mobile cells may become fixed and either retain in the sessile state their special phagocytic properties or lose these entirely and become converted into the ordinary connective tissue elements—fibroblasts—or into epithelioid cells. The fibroblasts, however, never undergo the reverse change and assume ameboid characters; once formed they remain fixed. According to Maximow, lymphocytes may give rise to macrophages. The latter, however, never give rise to lymphocytes.

In chronic inflammation or in the repair stage of an acute process, the histiocytes play an important rôle. Some (the so-called *dust cells* of the lung) are responsible for the removal of foreign particles which have been carried into the pulmonary alveoli by the inspired air. The ability of the Kupffer cells to take up ingested thorium dioxide (thorotrast) which is opaque to the

X rays is made use of to delineate the liver in the living subject. The spleen, placenta, ureter and kidney pelvis, the vessels of the extremities or of the brain and the cerebral ventricles, can also be outlined radiographically by means of this agent. The administration of thorotrast is not, however, free from danger. It is radioactive, the alpha ray activity of 25 cc. of thorotrast being equivalent to that of 1 microgram of radium which is sufficient to produce pathological changes in susceptible persons. Thorium dioxide is eliminated from the body in insignificant amounts, almost all being permanently stored in the reticulo-endothelial cells of the bone marrow, spleen and lungs, as well as in the Kupfer cells, and even though no deleterious effects result from its radioactive properties it sets up a proliferation of connective tissue by acting as foreign material.

The epithelioid and giant cells of certain specific inflammatory processes, e.g., tubercle, which are derived from the histiocytes is but another instance of the latter's protean nature, and it is owing to these activities that the tissues are rendered so remarkably adaptable and plastic in their reactions to altered conditions. The omentum for example has long enjoyed a reputation as a protective structure, owing to its ability to form adhesions which serve to seal perforations of the gastro-intestinal tract or to isolate infected regions within the abdominal cavity. The omental tissue is particularly richly supplied with both stationary and wandering histiocytes. It contains also, even in health, immense numbers of lymphocytes, which, in part, are derived from division of their own kind locally, and, in part, have come from the blood stream. Normally the presence of these various cells in such numbers gives an appearance closely resembling a defense reaction—the "physiological inflammation" of Rossie. Histiocytes and lymphocytes are continually being cast in showers into the peritoneal cavity at all times but to a much greater extent in irritative conditions. Monocytes have been studied in transparent chambers inserted into the tissue of the rabbit's ear. They have been observed to leave the circulation and to become motile and phagocytic, and otherwise indistinguishable from tissue histiocytes.

The formation of bile pigment (p. 459) and the final destruction of the blood cells (p. 56) in the spleen are other well established functions of the histiocytes. The reticulo-endothelial system is also believed to be concerned with antibody formation.

In certain pathological conditions, the lipemia of diabetes, Gaucher's disease and Niemann-Pick's disease (p. 56) the reticulo-endothelial elements, especially of the spleen, are markedly increased in number and become loaded with lipid material.

THE BLOOD-FORMING ORGANS OF POST-NATAL LIFE

Red cells, granulocytes and possibly platelets are formed in the bone marrow, and lymphocytes

in the lymphoid tissue. The stroma or reticulum of these structures is the essential blood-forming tissue. The latter consists of (1) a fine net of cylindrical or ribbon-like fibers which can be stained by silver preparations and (2) large *reticular cells*—which are fused together by branching processes to form a loose network; the latter is intimately associated with the network of (1) which appear as reinforcing strands. The *reticular cell* (embryonic reticular cell, p. 7) is the nearest approach in the adult body to the primitive mesenchyme cell. The blood-forming capacity of the myeloid and lymphoid tissues depends upon the ability of these cells to become hemocytoblasts which in turn, according to the environment in which they are situated, are capable of developing into red cells, granulocytes, megakaryocytes on the one hand or lymphocytes on the other.

THE BONE MARROW

It is the red marrow situated in the ends of the shafts of the long bones such as the femur, humerus, and to a greater extent in the sternum, vertebral bodies and cranial diploë in which the blood forming functions are performed (fig. 1). The total volume of the red marrow of the body equals or exceeds that of the liver. It amounts to about 1400 cc. The shafts of the long bones are filled for the most part with yellow marrow, composed of connective tissue and fat; this is non-hemopoietic. In early childhood red marrow occupies the medullary cavity of the long bones and even in adult life the fatty marrow retains the essential reticular structure of hemopoietic tissue and so is capable of blossoming into red marrow under suitable stimulation. So, under certain conditions, for example in pernicious anemia, up to a much less extent during residence at high altitudes, the red marrow is increased in amount. It encroaches upon the medullary cavity of the shaft replacing to a greater or less degree the fatty tissue.¹ In aplastic anemia on the other hand the fatty marrow increases at the expense of the red marrow.

Drinker has shown that the circulation of the marrow is closed, i.e., the blood and the reticular tissue are separated by a complete membrane. This is contrary to the older view that the blood

¹ In some cases of rapidly developing anemia droplets may appear in the peripheral blood, and in some cases of hemorrhage the fatty acids of the blood increase. These facts suggest a dispersal of the medullary fat in order to make room for an extension of blood forming tissue—the red marrow.

into direct contact with the marrow cells through gaps in the capillary walls. The vascular bed of the marrow is a mesh-work of small blood spaces (sinusoids) lined by flat endothelial-like cells similar in character to those lining the sinuses of the spleen (p. 55). Not all the sinusoids, however, are open at one time. It has been estimated

Doan that the marrow contains a great many more of these vessels than could possibly be accommodated within the resistant bony encasement, where they all in the dilated state. Some of the sinusoids are completely collapsed and impervious to the blood. Others are dilated but, owing to

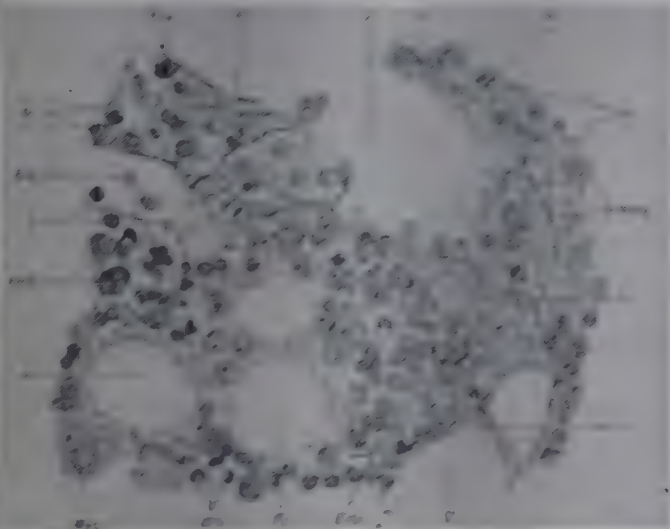


FIG. 27. Bone marrow from the upper epiphysis of femur of a child of six years; *a*, the fibrous network of the wall of a vessel from the surface and, *b*, in cross section; *c*, lining cells of the sinuses (littoral cells); *Emy*, eosinophil myelocyte; *Eos*, eosinophil leucocytes; *Erb*, erythroblast; *Erc*, erythrocytes; *Fc*, fat cells; *Meg*, mega karyocyte; *Nlk*, neutrophil leucocytes; *Nmy*, neutrophil myelocytes; *R*, reticular fibers (black with silver); *Sc*, nuclei of the primitive reticular cells; *V*, venous sinusoids (after Maximow and Bloom).

the vessels which lead to and from them being constricted, they are isolated from the general circulation. Regions of low oxygen tension are in this way provided. It has already been pointed out (p. 9) that a low oxygen tension serves as a stimulus to red cell formation.

The blood cells, if the observations of Maximow be accepted, are formed extravascularly and subsequently enter the blood stream.² Their pressure upon the endothelial wall causes its erosion or rupture and the cells invade en masse the lumen of the sinusoid where further growth and maturation of the cells follows. Finally through the

² Sabin, Doan and others contend that only the granulocytes have an extravascular origin, the erythrocytes being derived, not from reticular cells but from the endothelial elements (littoral cells of Maximow) of the marrow capillaries.

opening up at certain periods of the vessels leading from the hemopoietic region, the mature cells escape into the general circulation. The sudden showers of young cells that occur in pernicious anemia (blood crises) may be explained by a process of this nature. That the delivery of red cells into the circulation is normally intermittent is also suggested by the fact that the red cell count is not constant but shows a diurnal rhythm the highest counts occurring in the morning hours. There may be a difference of 300,000 cells or so between the maximal and minimal daily levels of the red cell count. Normally no cells enter the general blood stream until maturation is practically complete. Drinker for instance was unable to cause the passage of immature forms into the blood by prolonged perfusion of the marrow or by muscular exercise. The perfusion fluid evidently was unable to open a way into these isolated pools and wash out the immature forms. From the work of Krogh and of Lewis on the capillary circulation in other situations this result is not unexpected (p. 264).

THE MATURATION OF THE BLOOD CELLS

(a) Erythrocytes—Erythropoiesis

The red cells pass through several stages before they attain full maturity. In the examination of a simplified (hypoplastic) marrow, such as may be induced in the pigeon by underfeeding or in mammals after poisoning with benzol, most of the stages can be followed (cf. fig. 28 and frontispiece). The reticular cell, as we have seen, gives rise to the *hemocytoblast*. The latter divides into two daughter cells which stain deeply with basic dyes. These are called *basophilic erythroblasts* by Maximow; they contain no hemoglobin. The next stage which may be distinguished is, following Maximow's terminology, the *polychromatophil erythroblast*. The earliest cells of this stage are large, with a large, round and often vesicular nucleus; their cytoplasm is rich in basophilic material but also contains traces of hemoglobin. The hemoglobin concentration increases in amount as development advances, the more mature cells being well supplied with pigment. Hemoglobin is acidophilic, so the cells of the erythroblast stage, since they have retained a relatively large amount of basophilic substance, stain with both acid and basic dyes. This property of dual staining, known as *polychromasia*, diminishes again as the cells mature beyond the erythroblastic stage and gradually lose their basophilic material.

Several authors (Sabin, Dean and associates) distinguish three types of cells during this stage of development—the *megaloblast* and the *early* and *late erythroblasts*. The megaloblast of these authors corresponds to the youngest of the polychromatophil erythroblasts mentioned above, i.e., a large nucleated cell which, owing to its relatively large proportion of basophilic material, shows only a very slight tendency to polychromasia. Maximow avoids the term megaloblast, advising that it be reserved for the large cell of pernicious anemia to which it was originally applied. He claims that the latter cell, though resembling the primitive

in the marrow that they become discharged in the general blood stream.

In healthy marrow the multiplication of red cells which occurs to replace those lost from circulation through wear and tear is effected almost entirely by the division and redivision of late forms, i.e., of normoblasts and older erythroblasts (homoplastic development) and to a negligible extent through the multiplication and subsequent maturation of the more primitive forms. The youngest erythroblasts (megaloblasts), for example, in normal marrow are absent or amount no more than 0.01 to 0.04 per cent of the total nucleated red cell elements, according to Sabin; the older erythroblasts make up about 30 per cent and the normoblasts 70 per cent or so. In pernicious anemia, on the other hand, large numbers of megaloblasts are present. In this disease erythropoiesis appears to have reverted to a more primitive type—or, as it is expressed, “shifted to the left” (heteroplastic development). The benefits of liver therapy apparently depend upon the power of the hepatic principle to restore the normal mode of red cell development.

(b) Granulocytes—granulopoiesis

The earliest stage in the differentiation of the granulocytes from the primitive reticular cell in the marrow is that of the so-called *myeloblast*. It is generally agreed that the origin of the granulocytes is extravascular and that they pass into the marrow vessels only after they acquire motility. Maximow considers the myeloblast to be nothing more or less than the polyvalent hemocytoblast or stem cell, identical with the large lymphocyte, the minute differences in structure between it and the latter being due it is thought to the environment in which it is placed, i.e., the bone marrow. Here it gives rise to the three types of granulocytes. The myeloblast is given special interest since it is the predominant cell in the blood and marrow in certain forms of *leukemia* (p. 86) when it may constitute 90 per cent of the white cells. It constitutes only a very small percentage of the cells in normal marrow.

After the stage of the myeloblast a few specific granules begin to appear in the cytoplasm which at the same time becomes less basophilic in character. Also present are a few anisotropic granules. In the subsequent history of the cell up to its discharge into the circulation four stages, based upon the development of specific granulation and the reduction in basophilic material, are recognized. The cells of the first three of these stages

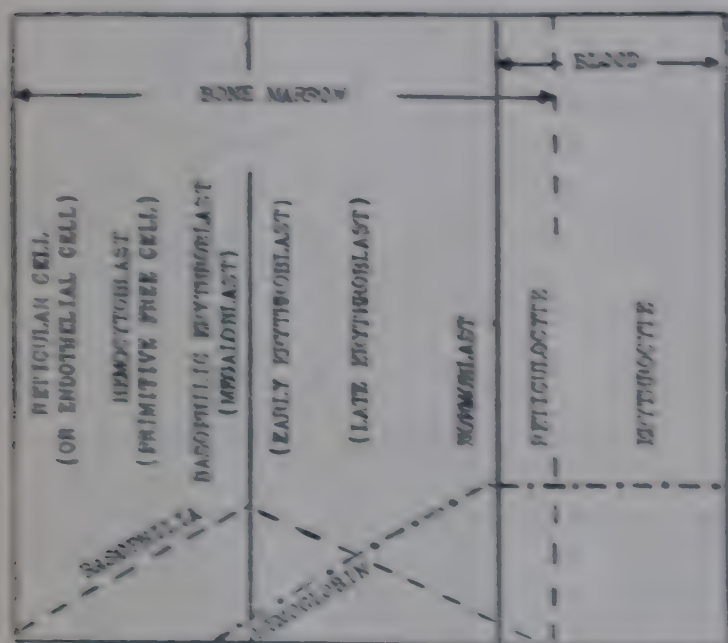


FIG. 28. Diagram showing maturation of the red cells. The view of Sabin, Dean and associates is indicated by the bracketed terms (see footnote, p. 85). As mentioned in the text the early and late erythroblasts of these observers are termed polychromatophil erythroblasts by Maximow. This term has been omitted from the diagram for the sake of simplicity provided from Sabin.

cell of normal marrow is probably not identical with it.

The older erythroblasts give rise to normoblasts. The normoblast, as the name itself implies, resembles the mature erythrocyte in size and hemoglobin content but still retains its nucleus which, however, shows condensation of its chromatin material (pyknosis) and stains more deeply. In the final stage of the maturation process, the nucleus is extruded from the cell and the now practically mature erythrocyte is discharged from the marrow into the general circulation. It betrays its youth only by a fine basophilic reticulation of its cytoplasm and is therefore called the *reticulocyte* (p. 12). It is probably not until the reticulocytes have reached a certain concentration

termed *myelocytes A, B and C*, respectively. Cells of the fourth stage are called *metamyelocytes* (fig. 29). In the youngest stage the granules, mentioned above, are very few³ and are in lesser numbers in myelocyte B and in maximum quantity in myelocyte C. The nucleus in these is oval or spherical and shows no attempt of lobulation. The metamyelocyte is characterized by slight indentation of the nucleus and the evidence of typical ameboid movement. Finally the nucleus becomes deeply indented or constricted at one or more points and is discharged into the circulation as a young leucocyte (neutrophil, eosinophil or basophil). This is the first stage of Arneith mentioned on page 71. It is also referred to by Schilling as the older metamyelocyte or the band cell. As shown in figure 29 three levels of development are distinguished. Level I extends from the reticular cell to, and includes, the myeloblast. Level II embraces the myelocyte and the metamyelocyte; cells at this level multiply actively and have the power of growth. Level III includes those forms present in normal blood (Arneith stages); the cells have lost the power to divide and grow.

The oxidase reaction (p. 73) depends upon the presence of specific granules. The myeloblast therefore does not give this reaction and the youngest myelocyte (A) responds in proportion to the number of granules which it contains; these may be very few and difficult of detection. The later myelocytes of course give a positive reaction. As in the case of erythropoiesis the earliest stages of white cell development—myeloblastic and early myelocytic—are little in evidence in normal myeloid tissue. The leucocytes are supplied to the blood through the division and redivision of the later forms of white cell elements—i.e., the myelocytes. A census taken of the colorless elements of the marrow in normal rabbits gives an average of about 1 per cent myeloblasts, 90 per cent myelocytes C and metamyelocytes, of which the great majority were neutrophilic, and about 10 per cent young leucocytes. Younger myelocytes make up the balance. The number of leucocytic elements is three times greater than the number of red cell elements—erythroblasts and normoblasts. The ratio of granulocytes to red cells in blood on the other hand, is 1 to 600. The differ-

This cell, myelocyte A, resembles so closely its progenitor the myeloblast and represents a transition stage between the latter cell and the older myelocyte that it is often referred to as the promyelocyte. Some use this latter term to include also myelocyte B.

ence in the cell ratios in marrow and in blood is ascribed to the greater mortality of the leucocytes and the consequent necessity for a greater hemopoietic activity in order to replace them.

In myeloid leukemia the process of granulopoiesis, is pushed back to a more embryonic type and immature forms appear in the blood. The marrow picture indicates a great activity of the early myelocytic and myeloblastic stages. The marrow of the fetus and to a less degree that of the new-born show also a relatively large proportion of immature cells.

(c) The platelets

These are generally stated to arise from giant cells of the marrow (40μ or more in diameter) known as megakaryocytes. The latter have an

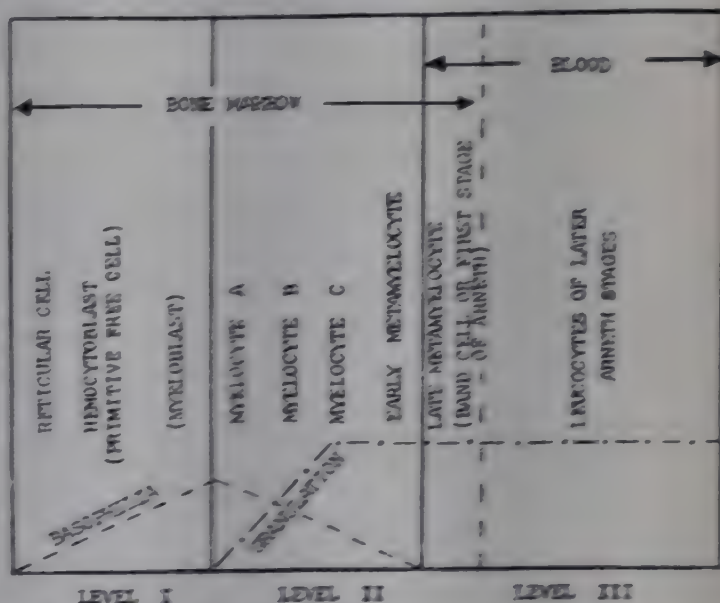


FIG. 29. Diagram showing maturation of the granulocytes. Bracketed terms are those of Sabin, Doan and associates (modified from Sabin).

irregular, ring-shaped nucleus, and are capable of ameboid movements. It was first suggested by Wright that fragments of their protoplasm became detached to form the blood platelets. Normally, the marrow contains only a few of these cells, but it has been stated that an increase or decrease in their number is followed by corresponding changes in the number of circulating platelets.⁴ Howell

⁴Wright's view of the origin of the platelets from megakaryocytes is not, however, universally accepted. Various views are held with regard to the genesis of the platelets, some believing them to be formed from the cytoplasm of leucocytes, and others that they are simply precipitates from the plasma. Several observers have expressed the belief that they are fragments of degenerated red cells. In support of this view Watson reports the observation that phenylhydrazine which damages the erythrocytes causes a sharp rise in the platelet count and a reduction in the number of red cells. This observer also found that, when erythro-

and Donahue have concluded from their experiments that the platelets are derived from megakaryocytes in the lungs. They base their view on the finding that both in cats and in man the platelet count is somewhat higher in arterial than in venous blood. The ratio of platelets to erythrocytes in arterial blood is 1:21.4, as compared with 1:25.8 in the blood of the corresponding vein, which implies that platelets are destroyed or removed from circulation in the capillaries and replenished in the lungs. Further evidence was derived from the observation that a smear of lung tissue shows large numbers of giant cells, whereas only a few are found in a similar specimen of bone marrow. It is probable, however, that the lung megakaryocytes do not originate in the lungs but have their source in the bone marrow and, owing to their large size, are merely trapped in the pulmonary capillaries.

(d) *Lymphoid tissue and the formation of lymphocytes*

The central areas of the follicles in lymphoid tissue (lymph glands, spleen, etc.) stain more lightly with the ordinary stains than the peripheral zones. These lighter areas, about 1 mm. in diameter and pierced near the center by a small arteriole, are generally known as the "germ centers." In the embryo and in new-born animals the earliest stage in the development of the lymphocytes is represented in lymphoid tissue as in the bone marrow by a large lymphocyte or hemocytoblast. It is analogous and practically identical in structure with the myeloblast. By some it is called the *lymphoblast*. It arises from the undifferentiated primitive reticular cell of the lymphoid stroma similar to that in the marrow from which the myeloblast and, according to Maximow, the erythroblast arise but as in the case of the myeloid cells the lymphocytes normally arise from the division of cells of later stages.

An interesting experiment of Maximow's supports the view that the large lymphocyte is the common precursor of the granulocyte and lymphocyte and that the course of development which

the stem cell shall follow is determined by its immediate environment. Lymphoid tissue was cultured in an environment prepared to simulate that of the bone marrow by the use of a preparation of blood plasma and marrow extract. Proliferation of the large lymphocytes and their differentiation into myelocytes were clearly observed.

(e) *The origin of monocytes (see p. 81)*

THE LEUKEMIAS

In these conditions the number of white cells usually enormously increased and may reach a count of 1,000,000 per cubic millimeter. The red cells are reduced.

On the basis of the type of white cell predominance in the blood two main forms of the disease are recognized—the *myeloid or myelogenous* and the *lymphatic*. Either of these may be chronic or acute.

MYELOID LEUKEMIA (SYNONYMS; MYELOGENOUS SPLENO-MEDULLARY, MYELOCYTIC LEUKEMIA)

In the *chronic form* the white cell count is very high, frequently running into the hundreds of thousands per cubic millimeter. The predominant cell is the neutrophilic myelocyte though eosinophilic and basophilic myelocytes and myeloblasts (2 to 3 per cent) are also present in smaller numbers. The spleen is enlarged, often greatly, and the yellow bone marrow is replaced by a grayish pink richly cellular tissue.

In the *acute form* of the disease the myeloblasts, or rather myelocytes A (promyelocytes) dominate the blood picture. The condition is usually referred to as *acute myeloblastic leukemia*. There is pronounced anemia and immature red cells appear in the blood.

LYMPHATIC LEUKEMIA

In the *chronic form* the predominant cell is the small lymphocyte. These average around 100,000 per cubic millimeter. Enlargement of the lymph glands and general hyperplasia of lymphoid tissue occur. The spleen is increased moderately in bulk.

In the *acute form* of lymphatic leukemia the blood contains large numbers of both small and large lymphocytes. These latter, according to Maximow's view, may be regarded as hemocytoblasts and so the forerunners of small lymphocytes just as the myelocytes found in myeloid leukemia is an immature granulocyte. Since the large lymphocyte and the myeloblast are identical, i.e., they are both hemocytoblasts exposed to different environmental conditions, it is very difficult to distinguish the so-called myeloblast (myelocyte A) in myeloblastic leukemia and the large lymphocytes in acute lymphatic leukemia. The oxidase reaction is sometimes employed in an effort to make the distinction but as a rule is unsuccessful since the youngest myelocytes also frequently fail to give a definitely positive response.

cytes were suspended in a counting chamber, degeneration of the red cells occurred while bodies indistinguishable from platelets appeared. Furthermore, the platelet count, as shown by Bodson, is increased by splenectomy, or by "blackening" the reticulo-endothelial macrophages (which, as we have seen, engulf red cell fragments) by injections of India ink. The term "blackening" refers to the overloading of the reticulo-endothelial cells with the ink particles and the consequent suppression of their phagocytic properties.

In some instances of leukemia the total white cell count is not increased (it may be diminished) but the proportion of lymphocytes or granulocytes, respectively, raised and immature forms appear. This variety of disease is spoken of as *a-leukemic leukemia*.

Monocytic leukemia is a third and unusual type of disease in which the blood picture is dominated by monocytes. These are recognized by supravital staining (p. 80) with neutral red—when a rosette-like arrangement of the dye particles appears in the cytoplasm. The oxidase reaction is of course negative.

PATHOGENESIS

The cause of leukemia is unknown. In the two common types of the disease—myeloid and lymphatic—

the formation of the immature cells in the majority of instances is concentrated respectively in bone marrow and lymphoid tissue. In the chronic myeloid form myelocytes are formed in the spleen as well. The great enlargement of the spleen in this form is due partly to the phagocytic activity of this organ which is called upon to remove a much greater number of degenerated leucocytes than usual and partly to the manufacture of immature cells. From what has been said in previous pages of the varied potentialities of the stem cell it is evident that either type of cell may also arise from any situation in the body in which reticular cells exist. Thus lymphocytes may arise in the lymphoid tissue of the spleen, or lymph nodes, or either type of cell may arise in the general connective tissues.

CHAPTER XII

THE COAGULATION (CLOTTING) OF BLOOD

GENERAL DESCRIPTION OF THE CLOTTING PROCESS

If blood be collected into a test tube it will be found at the end of 5 or 6 minutes that it has lost its fluidity and has set into a jelly. The tube may be inverted, but the blood, which is now said to have *clotted* or *coagulated*, does not escape. If it were possible to magnify this clot many times and to look within it, one would see a mesh of very delicate fibrils, among which were entangled, as in a net, the red and white cells and many fragmented platelets. The fibrils can be readily revealed if a thin section of the clot be examined under the high power of the microscope. They are composed of *fibrin* formed by the conversion of the fibrinogen from a soluble (hydrosol) into an insoluble form (hydrogel). The fibrin as it forms is deposited as very fine needle-shaped crystals. If the clot is permitted to stand for an hour or so, it will be found to have shrunk, and in shrinking to have expressed from its interstices a clear, faintly straw-colored fluid. This is the *serum*. The latter remains perfectly fluid and is totally incapable of clotting. The shrinking and condensation of the clot is due to the gradual shortening of the fibrin threads which enmesh the corpuscles. In this retraction of the clot or *syneresis*, as it is termed, the platelets play an essential rôle. Though numbers of platelets undergo disintegration when the blood is shed (see below), others become attached here and there in groups or knot-like clumps to the fibrin threads, and in some unexplained way cause bending and shortening of the latter. Clots formed in blood deficient in platelets are soft and friable, and do not contract in the normal way. It used to be thought that the intact platelets which were seen in sections of blood clots served as nuclei from which the fibrinogen to fibrin conversion started, but it has been demonstrated by Tocantins that the platelets take up their positions *after* the fibrin has formed. The full retraction of the clot and the separation of the serum ordinarily takes a considerable time, but separation can be brought about within a few minutes by rapid centrifuging.

If the blood be centrifuged as soon as it is shed and the cells in this way separated from the plasma, a clot forms in the latter, due as before to the formation of fibrin threads. After a time the

colorless clot shrinks and, as in the case of whole blood, expresses the transparent serum. The clotting process is therefore essentially a phenomenon of the plasma. The so-called "buffy coat" which forms in the upper layers of blood when it clots slowly, and so allows a certain degree of sedimentation of the cellular elements to occur, is the clotted plasma.

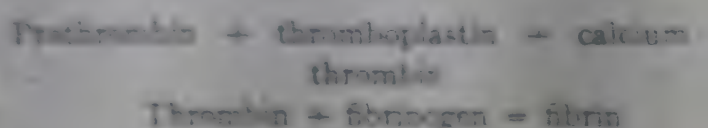
THE CLOTTING MECHANISM

In the very intricate mechanism underlying the coagulation of blood the following substances take part. (1) *Prothrombin*, (2) *thrombin*, (3) *thromboplastin* (or *thrombokinase*), (4) *ionic calcium* and (5) *fibrinogen*. By the action of thromboplastin, prothrombin, which is inactive, is converted in the presence of calcium ions into the active thrombin. Thrombin, an enzyme, then acts upon the soluble fibrinogen of the plasma to convert it into the insoluble fibrin spoken of above, forming threads in which the solid elements of the blood are enmeshed. Thus the clot is formed.

Under normal circumstances the blood remains fluid in the vessels not, as was thought at one time, because it is in motion, but most probably because thromboplastin is present in circulating blood in only very small amounts and, as a consequence, the active enzyme thrombin is not produced and fibrin is not formed. Any small amount of thrombin which might arise in the blood is neutralized by an antithrombin. This latter material, the so-called *normal antithrombin* of the plasma, is present in low concentration in mammalian blood but in much larger quantities in the blood of birds. According to Quick, it is closely associated with the albumin fraction of the plasma.

When blood is shed, thromboplastin is liberated from the injured tissues or from the fragmentation of platelets, thus the clotting mechanism is initiated.

The modern conception of the clotting process is outlined in its simplest possible terms in the following scheme.



s, only four *primary factors*, prothrombin, thromboplastin, ionized calcium and fibrinogen are required for the coagulation of blood.)

Ferguson found that during the process of activation of prothrombin by calcium and thromboplastin, there is a stage lasting for a few minutes in which the removal of calcium (by the addition of oxalate) causes inactivation of the newly formed product ("fresh" thrombin). After the thrombin is fully elaborated ("ripe" thrombin), except for a slight delay just mentioned, the removal of calcium ions does not affect the coagulant action. He believes that this difference in the effect of calcium lack upon "fresh" and "ripe" thrombin indicates the formation of an intermediate complex in the production of thrombin from prothrombin. Ferguson concludes that thrombin is a calcium-thromboplastin-prothrombin complex or compound.

Heparin. (The action of certain impure extracts of liver in inhibiting the coagulation of blood was discovered by McLean, a pupil of Howell, in 1916. Later, a series of studies was carried out by Howell and Holt upon extracts of liver from which they obtained a powerful anticoagulant. They gave it the appropriate name of *heparin*. Howell and Holt obtained their material from dog's liver, but it has since been prepared in larger quantities by Charles and Scott from beef liver. Lung, muscle and intestinal wall also contain it in relatively large amounts. Smaller quantities are contained in spleen, heart and thymus. It is present in negligible quantities in serum. When heparin is injected into the living animal the blood remains incoagulable for many hours. A unit of heparin is defined as the quantity of material which will prevent for 4 hours the clotting of 1 cc. of cats' blood when kept in the cold. A very potent crystalline preparation has been obtained from beef liver by Scott and Charles. This contains nearly 100 units per milligram.)

Jorpes found that like certain other anticoagulants, such as azo dyes and germanin, the heparin molecule contains sulphuric acid groups, in virtue of which it acts as a relatively strong acid. It belongs to the same chemical group as that to which mucic acid and chondroitin sulphuric acids belong. Anticoagulants have been prepared by Chargaff and his associates by the introduction of sulphuric acid groups into such polysaccharides as cellulose, glycogen and starch and into the cerebrosides, cerebrin and kersin.

The anticoagulant action of heparin is due mainly to its being a powerful *antithrombin*, i.e., its property of inactivating thrombin. Its

antiprotrombin action, i.e., its ability to prevent or inhibit the conversion of prothrombin to thrombin has been doubted, but the experiments of Ferguson provide evidence for such an action which is due apparently to its neutralization of the action of thromboplastin—an essential factor in the initial phase of the clotting process. Thromboplastin also neutralizes the antithrombin action of heparin. Therefore, when thrombin and heparin are present in suitable proportions to maintain the fluidity of a sample of blood, the addition of thromboplastin causes coagulation. The result is not influenced by the presence of calcium salts.

Heparin is present only in minute amounts in the circulation, and at any rate is not responsible for the maintenance of the fluidity of the blood in the living body. The most probable reasons that the blood does not clot intravascularly is, as already mentioned, because thromboplastic material is not available in sufficient amounts to convert the prothrombin to thrombin and because an antithrombin other than heparin exists in the circulating blood.¹

From the evidence procured by Wilander, heparin appears to be a product of the mast cells (mobile basophil cells of the tissues) which may be seen in clusters around the minute vessels of those tissues which give a high yield of heparin. Mellanby suggests that the significance of heparin in tissues is that it serves as a *local* anticoagulant, preventing the clotting of blood in the small vessels.

Chargaff and Olson found that protamine (salmine) annuls the action of heparin both *in vitro* and *in vivo*. Protamine, a simple protein with basic properties (see also p. 539 and p. 580) combines with heparin, the resulting compound being free from anticoagulant action. Thus it is possible to determine the quantity of heparin in a sample of blood by ascertaining the quantity of protamine required to give the shortest coagulation time. By this means the great lengthening of the coagulation time in anaphylaxis (up to 2 days or more) and peptone shock has been shown by Waters, Markowitz and Jaques to be due to the high concentration of heparin in the circulation (p. 92). Heparin is most effective when admin-

¹ According to Quick, heparin does not in itself act as an antithrombin but merely intensifies the action of the normal antithrombin of blood (namely, serum albumin) to produce a powerful anticoagulant. Quick also claims that heparin is not neutralized directly by thromboplastin but that the apparent neutralization is due to the acceleration by thromboplastin of the production of thrombin from prothrombin.

istered intravenously, much larger doses being required when it is given by subcutaneous injections. Besides its action in prolonging the coagulation time, heparin, as shown by Murray, Jaques, Perrett and Best, hinders the agglutination and deposition of platelets and thus discourages thrombus formation. Heparin has been recognized for a number of years as a valuable anticoagulant for use in physiological experiments but it is only comparatively recently that purified preparations suitable for clinical use have become available. Its most important field of usefulness is in blood transfusions, in operations upon the blood vessels and to check the extension of certain types of thrombosis. Its employment as a preventive against postoperative and other thrombotic conditions which carry the threat of fatal pulmonary embolism (p. 96) has been advocated by several investigators (Howell, Mason, Hedenius, and Murray and associates). Widstrom and Wilander have suggested its use to prevent the formation of fibrinous adhesions in pleurisy; in heparinized rabbits the inflammatory exudate caused by the injection of iodine into the pleural cavity is incoagulable.)

THE PROPERTIES OF PROTHROMBIN AND THROMBIN AND OF THROMBOPLASTIN

Prothrombin and thrombin, according to Seegers, are carbohydrate-containing proteins. This investigator has prepared from beef plasma highly potent preparations of these agents which contain, respectively, 300 units of prothrombin activity and 600 units of thrombin activity per milligram. At a pH of 7.0 prothrombin and thrombin are highly soluble in water or physiological saline, it being possible to prepare a 60 per cent solution of either material. Prothrombin is insoluble at a pH of 4.9 and thrombin at about 4.3. Both substances are completely and permanently inactivated by acid (pH 3.5) and by alkali (pH 11.0). They are destroyed by heating to 60°C. for 30 minutes.

Quick has secured evidence that prothrombin is a complex, consisting of two components (A and B) combined through calcium. Component A is reduced, presumably through oxidation, by oxalate. Component B is destroyed by dicumarol, and possibly also as a result of a deficiency of vitamin K. Component A disappears from stored plasma. In hypoprothrombinemia it is usually only component B which is reduced.

The origin of prothrombin. The liver is probably the chief source of prothrombin, though the experi-

ments of Drinker point to its being produced to some extent as well by the bone marrow. This observer obtained a fluid rich in prothrombin by perfusion of the bone marrow. The production of prothrombin is governed by vitamin K (p. 660).

Thromboplastin is present in all tissues, lung and brain being especially rich sources. It is soluble in fat solvents and, according to Howell, is identical with or closely allied to the phospholipid, *cephalin*.

HEMORRHAGIC TENDENCIES DUE TO HYPOPROTHROMBINEMIA

Depression of the prothrombin level in the blood—*hypoprothrombinemia*—occurs under several conditions, such as vitamin K deficiency and severe liver damage. A bleeding tendency is not shown, however, according to Quick, until the prothrombin concentration falls to about 20 per cent of the normal. Other observers, however, place the critical level somewhat higher.

Hemorrhagic disease of the newborn has been shown quite definitely to be the result of a low prothrombin concentration. At birth and up to 6 hours thereafter, the prothrombin level is not far below normal, but apparently the baby comes into the world with a small reserve. This tends to become quickly exhausted, so that the prothrombin concentration may reach a dangerously low level at the end of 24 hours. This physiological hypoprothrombinemia is due to lack of vitamin K. When the infant commences to take food, bacteria are introduced into the intestinal tract which, acting upon the contents of the intestine, synthesize the anti-hemorrhagic vitamin (p. 660) and the hypoprothrombinemia is corrected automatically. Should the hemorrhagic state develop it is quickly arrested by the administration of vitamin K. Large doses may be given to the mother in the later months of pregnancy as a preventive. Hypoprothrombinemia and a hemorrhagic tendency also occur in diseases, e.g., acute yellow atrophy, associated with severe liver damage, in certain intestinal diseases, e.g., sprue and ulcerative colitis, and in the hemorrhagic disease of farm animals caused by eating spoiled sweet clover. In the animal disease the low prothrombin level is due to a toxic substance (*dicumarol*). The mode of action of this agent is not altogether clear. In therapeutic doses it does not damage the liver, though in large doses it may, and its anticoagulant action is then enhanced as a result of the depression of prothrombin production. Quick states that it reduces the B component of prothrombin.

The bleeding tendency which for years has been recognized to be a feature of obstructive jaundice or when bile is lost to the exterior through a biliary fistula has been shown to be the result of vitamin K lack. The deficiency is not due, however, to any dearth of the vitamin in the intestinal tract, but simply to the absence of bile salts without which the vitamin cannot be absorbed into the blood stream (p. 660). The prothrombin disappears from blood stored for transfusion purposes but it is questionable whether the fact is of much practical importance, provided that the production of this factor by the liver is not depressed.

Determination of the shortened coagulation time as an index of the prothrombin concentration. Prothrombin time. Quick's method is as follows. Nine volumes (about 5 cc.) of blood obtained from a vein is decalcified (p. 000) by the addition of one volume of a 0.1 mol solution of sodium oxalate. In a small test tube 0.1 cc. of the oxalated plasma is mixed with 0.1 cc. of thromboplastic material (prepared from fresh rabbit's brain or viper venom) and recalcified with 0.1 cc. of 0.025 mol solution of calcium chloride. The time from the addition of the calcium to when the clot forms is recorded by a stop watch. The test is carried out in a water bath at 37.5°C. The prothrombin concentration in per cent of the normal is calculated as follows:

$$\text{Prothrombin concentration} = \frac{K}{\text{c.t.} - a}$$

c.t. = clotting time; K, a constant = 302; a, a second constant = 8.7. Thus if the clotting time is 21 seconds the prothrombin concentration is $\frac{302}{21 - 8.7} = 25$ per cent of normal (approx.).

The prothrombin time is now utilized as a test for liver function.

The means used to prevent or retard coagulation—anticoagulants

(1) COLD. Since blood clotting involves the action of enzymes it is to be expected that coagulation will be retarded by lowering the temperature. Keeping blood at a temperature of from 5° to 10°C. postpones coagulation but does not absolutely prevent its occurrence. Cold, e.g., ice, etc., applied to the surface of the body as a measure for the arrest of hemorrhage has however little if any influence in retarding the coagulation process. As a matter of fact a hemostatic effect is brought about in such instances as a result of the vasoconstriction reflexly induced.

(2) AVOIDANCE OF CONTACT BETWEEN THE BLOOD AND FOREIGN MATERIALS OR INJURED TISSUES. Since thromboplastin is essential for blood coagulation any measure that will prevent injury to the platelets or that will prevent the blood from coming into contact

with the tissues will retard the clotting process. Receiving the blood directly from an artery or vein into a glass vessel free from dust or foreign material of any sort, especially if the inner surface be made smooth by a coating of paraffin, will slow the coagulation process. By this means the disintegration of the blood platelets is reduced to a minimum and contact with the tissue cells is avoided. The blood of birds collected in this way remains fluid indefinitely. That the necessary thromboplastin is present in the blood, but that some special means are required for its liberation, is shown by the fact that upon the addition of a small quantity of distilled water or of foreign particles to the drawn blood clotting at once ensues.

On the other hand, if the blood flows over a rough surface it causes greater fragmentation of the platelets and so hastens coagulation. The blood coming from a ragged wound which involves a greater destruction of tissue, is also likely to clot more quickly than if it issues from a blood vessel that has been cleanly incised, as by a scalpel or a razor. The contact of a sponge or a powdered substance to the wound by increasing the extent of surface exposed also hastens the formation of the clot.

(3) DE-CALCIFICATION OF THE CLOTTING MECHANISM. The addition of oxalate (sodium, potassium or ammonium) or of a fluoride to blood to the extent of 0.1 per cent or more completely destroys its power to clot spontaneously. In the former instance the calcium is precipitated as calcium oxalate. Oxalated blood recovers its ability to clot if shaken with chloroform, but the fibrin which forms redissolves after the blood has stood for a time. Fluoride does not precipitate the calcium but forms a weakly dissociated calcium compound. Sodium citrate also prevents coagulation. In this instance a double salt—calcium sodium citrate—is formed which again is only slightly dissociated. If calcium in the ionic form, e.g., the chloride, be added to the oxalated, fluoride or citrated plasma (recalcification), the power of the blood to clot is regained. Also the addition of thrombin or of thromboplastin to the decalcified blood causes it to clot. The restraining effect of citrates upon the clotting process was made use of during the last war for transfusion purposes. The donor's blood was received into a special transfusion bottle containing isotonic sodium citrate solution. Oxalates and fluorides on account of their intensely poisonous properties cannot of course be used in transfusion.)

(4) NEUTRAL SALTS. Magnesium sulphate solution in a strength of 27 per cent mixed in the proportion of 1 to 4 of blood postpones coagulation for some time, but does not prevent it indefinitely. Sodium sulphate in half saturated solution added to an equal quantity of blood has a similar effect, as has also a 10 per cent solution of sodium chloride in the same proportion. The manner in which these substances act is not clear. They do not decalcify the blood. That the activity of some or other elements necessary for the clotting

process is merely suspended and that none are destroyed, is shown by the fact that mere dilution of the "salted" blood is followed by clotting. Some think that these substances may act by preserving the platelets and corpuscles from disintegration and so hindering the liberation of thromboplastin. Zinc sulphate in 0.5 per cent solution prevents coagulation by precipitation of the fibrinogen. Sodium thiosulphate and germanin are anticoagulant, this action depending apparently upon their sulphur content.

(5) AZO-DYES, such as Chicago blue 6 B, Trypan red, Trypan blue, Chlorazol fast pink B.K.S. etc., are powerfully anticoagulant. Chicago blue, the anticoagulant property of which was discovered by Rous and his associates in 1930, is more potent either *in vivo* or *in vitro* than the earlier preparations of heparin. One milligram of purified Chicago blue will prevent for 60 hours the coagulation of 1 cc. of rabbit's blood kept on ice.

(6) CERTAIN SUBSTANCES OF A BIOLOGICAL NATURE.

(a) *Hirudin*, a substance secreted by the buccal glands of the leech and extracted commercially has a very powerful anticoagulant effect. It is a typical anti-thrombin, i.e., like heparin, it inactivates thrombin. *Hirudin* has been used extensively in the past to prevent coagulation during physiological experiments. (b) *Snake venoms*. The poisons of some snakes, particularly of the cobra, are powerfully anticoagulant. One hundredth part of a milligram per kilo of body weight will, according to Howell, entirely prevent coagulation. Its anticoagulant effect is thought to be due to some chemical change which is produced in the thromboplastin. The anticoagulant effect of cobra venom is probably intimately associated with its hemolytic action (p. 50). Some other snake venoms, however, have just the reverse effect and cause intravascular clotting. (c) *Heparin* (see p. 89). It is the most powerful of all anticoagulants of animal origin, being several times more effective than *hirudin*. (d) *Peptone solution* when injected prevents coagulation. According to Howell it acts by stimulating the liberation of heparin from the liver. Confirmatory evidence for this explanation has been furnished by others (Quick, and Waters and associates). Peptones also have an anticoagulant action when added to shed blood. The anticoagulant effect under these circumstances is ascribed by Mills and by Pickering to the increased resistance of the platelets to disintegration induced by the peptone solution. (e) In *anaphylactic shock* the blood remains incoagulable indefinitely (up to 2 days at least). Waters, Markowitz and Jaques have shown that this is due to the liberation of heparin from the liver. Anaphylaxis produced in hepatectomized dogs is not accompanied by a prolonged coagulation time. (f) *Cysteine* (see p. 466). (g) *Dicumarol*, an anticoagulant found in spoiled sweet clover. This material exerts its action by depressing the prothrombin concentration (p. 90).

Defibrinated blood

If blood be kept constantly stirred or be whipped by means of a faggot of fine twigs or wires, the fibrin gradually collects upon their surfaces. In this way all the fibrinogen in a short time becomes converted into fibrin which is removed as it is formed. The fluid which remains is composed of serum together with the red and white cells and resembles blood in appearance and consistency, but of course is totally incapable of clotting. Defibrinated blood is frequently used in physiological experiments instead of employing an anticoagulant. Though defibrinated blood closely resembles ordinary blood it frequently contains toxic substances developed during the clotting process and is, therefore, unsuitable for transfusion into man. The formation of fibrin is actually hastened by the whipping action, since the greater surface to which the blood is exposed and the violent agitation to which the cellular elements are subjected cause a more rapid abundant liberation of thromboplastin. Blood which has been extravasated into the pleural, peritoneal or other body cavity is usually found to be fluid, if any considerable time has elapsed since the hemorrhage occurred. Such blood is found to be incoagulable, for it has already clotted and then undergone a natural process of defibrination, the clots having been dissolved as a result of the digestion of the fibrin (fibrinolysis) by proteolytic enzymes. The fluidity of menstrual blood is caused in the same way. A fibrinolysin, although not present in normal blood under ordinary circumstances, appears in plasma after shaking with chloroform.

Substances which hasten the clotting process

(Adrenaline when injected hastens the clotting process. Emotional excitement, muscular exercise and hemorrhage act similarly probably through the liberation of the hormone from the adrenal medulla. Adrenaline has no effect upon the coagulation of blood after it has been shed.

The effects of thrombin and thromboplastin have been discussed. Tissue extracts especially those of lung and thymus which are rich in thromboplastin are powerfully coagulant, as are also the venoms of some species of snakes. The coagulant property of such venoms depends upon their containing a proteolytic enzyme which converts prothrombin to thrombin; the conversion occurs in the absence of ionized calcium.

Repeated injections of sodium citrate are also said to increase blood coagulability through the compensatory production, it is supposed, of a coagulant material within the body. Repeated injections of oxalates have a similar action.

COAGULATION TIME

(The coagulation time is the time which the blood takes to clot after it has been shed. Obviously, any condition which decreases the coagulability

the blood lengthens the coagulation time and vice versa.

A number of methods have been devised to determine the precise moment when clotting occurs. The clotting time as determined by different methods varies considerably since the index or criterion of coagulation is not the same in all, and the conditions to which the blood is subjected are also different. On this account the values are not absolute and the results obtained by different methods cannot be compared strictly with one another.

A simple but rough method when a considerable quantity of blood is available is to collect the blood into a small test tube and take as the coagulation time, the period elapsing from the moment the blood is shed to when it congeals, as indicated by the inversion of the tube.

A more accurate method and one which requires only a drop of blood is the following. The blood is drawn into a capillary glass tube about 4 or 5 inches long. A section of the tube is broken off from time to time. The time elapsing from the moment at which the wound was made to that when fine threads of fibrin appear between the ends of the broken sections of the tube is taken as the coagulation time. The normal coagulation time by this method is about 4 minutes. There are many other methods for determining the coagulation time, e.g., Brodie's, Gibbs', Cannon and Mendenhall's, etc., but all have their defects and the foregoing is probably just as accurate as more elaborate procedures.

Clot retraction time. This is measured by collecting a few cubic centimeters of blood into a test tube. After clotting has occurred the clot is separated from the walls of the tube by means of a fine wire and the tube placed in an incubator set at a temperature of 37°C. The clot of blood retracts to a firm mass, the serum separating out within a couple of hours. In certain types of purpura (thrombocytopenic) the clot remains bulky, soft and friable. In hemophilia, on the contrary, when clotting does occur, the clot usually retracts normally.

THE BLEEDING TIME

The determination of the bleeding time simply consists in pricking the skin and noting the time the drop of blood takes to clot sufficiently in order to close the puncture in the skin and stop the bleeding. The precise moment when bleeding ceases is determined by touching the blood from the tiny wound every few seconds with a piece of filter paper. The moment when the latter ceases to be stained is taken as the end point. The normal

bleeding time is about 2½ minutes.² One might suppose that the bleeding time would be a better gauge of the body's ability to protect itself against hemorrhage than the coagulation time, but the fact that it is normal, as a rule, in hemophilia (see below) shows that this is not so. Actually, there is little relationship between the bleeding time and the coagulation time. The former is prolonged in conditions associated with low platelet counts. It is shortened by the local application or intravenous injection of platelet extracts, by the application of solutions with a low pH (around 5), or by the injection of posterior pituitary extracts. Ordinary hemostatics either have no effect or prolong the bleeding time.)

DISEASES ASSOCIATED WITH ALTERED COAGULABILITY OF THE BLOOD

Hemorrhagic tendencies due to a low prothrombin concentration have been mentioned (p. 90). A fibrinogen defect is a rare cause of bleeding. There may be a congenital lack of this plasma protein, amounting even to its complete absence. It is well to emphasize here that a low serum calcium is never a causative factor in hemorrhagic diseases. In hypoparathyroidism in which the serum calcium may be depressed to less than half the normal value the coagulation time is not lengthened.

Hemophilia

The coagulation time but not the bleeding time as defined above is greatly prolonged in this condition.³ In some cases the blood after removal from the body may show no signs of clotting after an hour or so. On this account a fatal hemorrhage may follow a wound that would be trivial in a normal person. The extraction of a tooth, a slight accident or a minor operation has resulted in death on many occasions. The subjects of this disease

² Ivy and his associates recommend first raising the venous pressure in the arm by constricting it above the point where the skin puncture is to be made. A constricting pressure of about 40 mm. Hg is applied. Tocantins has devised an instrument which makes an incision of approximately uniform length and depth.

³ Not every person with a tendency to bleed can be classed as a hemophilic. True hemophilia answers to the following criteria.

- (a) Males only.
- (b) History showing characteristic type of inheritance.
- (c) Coagulation time of drawn blood, but not the bleeding time, is greatly delayed.
- (d) No reduction in platelets, but these show lessened fragility.
- (e) Quick's test positive.

are known popularly as "bleeders." Hemophilia is transmitted as a sex-linked recessive character. The males are affected but do not transmit the disease; the females, though they transmit the disease do not suffer themselves (law of Nasse (1820)). A father then, who is a "bleeder" does not transmit the disease to his children in a manifest form. His sons are entirely free from any taint but his daughters inherit the disease in a masked or latent form and transmit it to their offspring. Of these the males show the disease, and the daughters again are not "bleeders" but are "carriers" for the next generation. In other words the disease skips a generation. Some of these bleeder families have been traced back for a hundred years or so and cover in some cases 5 generations and hundreds of individuals. The incidence of the disease in these instances followed in general the plan outlined above. It is theoretically possible should a "bleeder" and a "transmitter" marry, for the female as well as the male children to be "bleeders." Such a coincidence must be so very rare that for practical purposes it may be said that true hemophilia never occurs in the female.

The essential defect in hemophilia is a deficiency of thromboplastin due, it is thought, to an abnormal stability of the platelets. The conversion of prothrombin to thrombin is therefore retarded. Quick has devised a test for hemophilia based apparently on the resistance of the platelets to fragmentation. The plasma of a suspected hemophilic is rendered incoagulable by the addition of 0.5 cc. of a 0.1 molar solution of sodium oxalate. The oxalated plasma is divided into two equal portions. One half is centrifuged at 1000, the other at 3000 revolutions per minute. The two samples are then recalcified by the addition of 0.2 cc. of a 0.0125 molar solution of calcium chloride. The portion centrifuged at the higher rate will be found to have a considerably shorter clotting time than that portion centrifuged at the lower rate. The clotting time of normal plasma, on the contrary, is not affected significantly by the speed of centrifugation, both samples clotting at approximately the same time following recalcification. The other factors concerned in the coagulation mechanism appear to be normal. The calcium, prothrombin or fibrinogen is not diminished and heparin has not been shown to be increased. The logical corrective measure in persistent bleeding from this cause, is blood transfusion or the direct application of tissue extract or of healthy blood to the bleeding point. Barnett

and Macfarlane have reported a series of cases in which highly successful results were obtained from the application of snake venom to the wound. A 1 in 10,000 solution of venom of Russell's viper was used.

A bleeding tendency is sometimes seen in women but it differs from true hemophilia in that there is a prolonged bleeding time and the typical family history is absent. Quick's test is negative.

Purpura

This is a term applied to a variety of hemorrhagic states in which spontaneous bleeding occurs beneath the skin, from the mucous membranes or into joints. The subcutaneous hemorrhages appear as small or large purplish spots (*petechiae* and *ecchymoses* respectively) which gradually pass through the color changes characteristic of a bruise. Since purpura is so varied in its characters and occurs in diseased states that are so widely different, it should be considered as a symptom of a disorder of the blood-vascular system rather than as a disease in itself. It occurs in the malignant forms of many acute diseases—smallpox, scarlet fever, diphtheria, streptococcal infections, etc. Subcutaneous and submucous hemorrhages are also features of scurvy, leukemia, certain anemias and of the action of various toxic agents, e.g., snake venoms, drugs and chemicals. In some types of purpura (e.g., infectious and toxic forms) *deterioration of the capillary wall* probably plays the chief rôle—the red cells escaping into the subcutaneous tissues or from the mucous membranes through capillary defects. On the other hand a *great reduction in platelets* appears to be an important if not the essential defect in other types and a condition resembling purpura hemorrhagica (see below) has been induced in animals by the injection of an antibody developed for the destruction of platelets. Nevertheless the experiments of Bedson suggest that reduction of platelets or even their entire absence is not capable alone of inducing purpura. Some injury to the capillary wall must co-exist. This observer also found that splenectomized guinea pigs were highly resistant to the action of the anti-platelet serum. A theory has been advanced which relates the capillary defects to platelet reduction. It is probable that the platelets serve, normally, to protect the capillary wall and, by their deposition upon the endothelium, act as a seal against the escape of red cells through weakened points which are constantly occurring from general wear and tear. The reduction in platelets may result from several causes. There

may be increased destruction of these elements or the normal mechanism of their production may be interfered with, as in aplastic anemia and leukemia.

The coagulation time in purpura is usually within normal limits but the bleeding time is as a rule prolonged. The clot which forms in the blood after it has been shed is said to be softer than the normal and does not contract and express the serum in the usual way.

THE CAPILLARY RESISTANCE TEST. When cutaneous purpuric spots do not occur spontaneously they may be induced in susceptible persons by means of a tourniquet or blood pressure cuff applied to the upper arm so as to obstruct the venous return but not the artery. The obstruction is maintained for 5 minutes. In scurvy and other conditions associated with weakness of the capillary membrane the increased intracapillary pressure so induced results in the formation of small hemorrhagic points (petechiae) beneath the skin of the forearm. A more precise method consists of the application to the skin (usually of the forearm just below the antecubital fossa) of a small suction cup and determining the minimum negative pressure which, when applied for one minute, is required to produce petechiae. In health this lies between -200 and -300 mm. Hg. A minimum effective pressure less than -200 mm. Hg is abnormal.

Purpura hemorrhagica or Werlhof's disease (thrombocytopenic purpura) is associated with a great reduction in the platelet count. They may be almost absent from the circulation. Splenectomy is followed by an increase in platelets and frequently effects a cure. Recently snake venom has been successfully employed in the treatment of this disease. The observations of Troland and Lee point to the spleen in this disease as the source of a toxic material having a destructive action upon platelets. An acetone extract of the spleens of patients suffering from thrombocytopenic purpura upon injection into rabbits was followed by a prolonged fall (from 640,000 to 20,000 in 24 hours) in the platelet count. They have given the name *thrombocytopen* to the unidentified active principle in the extracts. Extracts prepared in the same way from normal spleens were without effect upon the platelet count. An abnormal number of megakaryocytes in the bone marrow especially of younger forms has been reported in purpura hemorrhagica and it is suggested that the failure of these to produce platelets is the fundamental fault.

In one form of purpura—*purpura fulminans*—the hemorrhages are exceptionally severe and the subcutaneous extravasations often extensive. Death may occur within a few days from loss of blood. In this state there is undoubtedly an affection of the capillary endothelium as well as reduction in the number of

thrombocytes. Purpuric manifestations may occur with more or less severe symptoms of gastro-intestinal irritation—*Henoch's purpura*—or in others bleeding into the joints (*Schonlein's disease*) is a prominent feature. In either of these forms the purpuric spots may occur in association with urticarial wheals or more generalized edematous swellings of the subcutaneous tissues. Capillary damage is probably either the essential or a contributory factor in these conditions.

Calcium is commonly employed in the treatment of the various types of purpura and appears to reduce the hemorrhagic tendency but the manner in which the effect is brought about is obscure; it is not through increasing the coagulability of the blood.

INTRAVASCULAR CLOTTING—THROMBOSIS

Coagulation within the vessels may be brought about experimentally: (a) By the injection of thrombin into the blood stream (see p. 92). Repeated injections of small amounts of thrombin cause the blood, after the first immediate increase of coagulability, to become for a few hours less coagulable than normal (negative phase). This is due apparently to the compensatory production of an antithrombin. No *permanent* reduction in coagulability can however be produced by repeated injections of thrombin over a period of several weeks. (b) By the rapid injection of a tissue extract (thromboplastin) particularly of the lung, thymus or lymph glands. This effect can be annulled by heparin. The repeated injection of *small* amounts of tissue extract has the reverse effect—decreased coagulability. This was shown by Mellanby and later by Mills and his associates to be the result of the gradual deposition of fibrin upon the vascular walls. The blood failed to clot simply because it had been depleted of fibrinogen. (c) By injury to the vessel wall either by chemical, mechanical or infective agencies, a roughened surface being thereby exposed to the blood stream. Thromboplastin is also liberated from the injured vascular wall.

Intravascular clotting involving areas of varying extent may occur in the human body from several causes. It is very doubtful whether this ever occurs as a direct result of an increase in any of those elements of the clotting mechanism normally present in the circulating blood, i.e., prothrombin, calcium or fibrinogen—or of a reduction in anti-thrombin (heparin). The increased liberation of thromboplastin which must result when tissue cells, whether of the blood vessels or other structures, are injured is probably, as suggested above, a factor under certain circumstances. The effect of this, however, is believed to be confined to the region in the immediate neighborhood of the

injury. It is unlikely that the liberated thromboplastin is capable of exerting an effect upon the blood as a whole, and cause clotting at a remote point in the vascular system.

The formation of a compact and solid mass of blood in a vessel (vein or artery) which partially or completely closes its lumen is spoken of as *thrombosis*. The plug itself is termed a *thrombus*. A thrombus may be formed simply by the clotting of the blood in the usual way, as occurs in an injured vessel. On the other hand the cellular elements of the blood may form a solid mass within a vessel and block its lumen independently of the clotting process. This occurs sometimes in the smaller vessels when the red cells become agglutinated into large clumps (agglutinative thrombus) as after the transfusion of incompatible blood. Once the vessel has become plugged in this way a true clot of course will form in the stagnant blood column. Owing to the slower blood flow in the veins it is in these vessels that thrombosis usually occurs.

When a thrombus, or a portion of it, becomes detached and carried away in the blood stream to become impacted in an artery at some remote point in the circulation, it is spoken of as an *embolus*. When arising from a venous thrombus the embolus is likely to lodge in a vessel of the lung. If formed in the left heart it may plug a cerebral vessel. The main vessel leading to a circumscribed area may become obstructed and the anastomosing channels be insufficient to maintain the nourishment of the tissue. The isolation of an area in this way by the obliteration of its artery is spoken of as *infarction*, and the necrotic area as an *infarct*.

Causes of thrombosis

The causes of thrombosis in the human subject may be grouped under the following heads.

(1) **INJURY TO THE VESSEL.** Complete mechanical obstruction of the circulation as by a ligature or pressure upon a vessel from without does not alone cause thrombosis. The latter is usually associated with some injury to the inner wall of the vessel; unless this occurs the blood may remain fluid for a considerable time.⁴ A thrombus, often very small in size, may form later

⁴ The importance of a smooth endothelial lining and the fact that stoppage of the blood stream alone does not necessarily cause clotting is demonstrated in the classical experiment of the "living test tube." If a section of the jugular vein of an animal, e.g., the horse, be isolated between ligatures and carefully removed with its contained blood, this will not clot for a long period, not until changes occur in the lining of the vessel wall and the necessary thrombokinase is thereby provided.

merely as the result of the slowing of the stream, the formation of eddies in the blind pocket and the deposition of platelets. Sometimes practically no thrombus is formed and the lumen of the vessel is obliterated by proliferation of the cells of the lining membrane.

(2) **AGGLUTINATION OF CORPUSCLES** (agglutinative thrombus).

(3) **TOXIC THROMBOSIS.** Certain chemical poisons, e.g., arsenical compounds, mercury, potassium chlorate, etc., may cause intravascular clotting. Poisonous mushrooms, certain snake venoms, as well as toxins formed within the body, as in eclampsia; or extensive burns, may induce thrombosis. The manner in which these various agencies act, whether by injury to the vessel wall, disintegration of blood elements, or through their effects upon some phase of the clotting process is obscure.

(4) **INFECTION BY MICROÖRGANISMS.** This is a common cause. The smooth endothelial lining is destroyed or roughened by the inflammatory process, thrombokinase is liberated from the injured tissues and disintegrated platelets. The latter probably also liberate prothrombin. Some degree of thrombosis is always associated with acute inflammatory processes of septic origin. The thrombosis may be strictly localized to the smaller vessels at the site of the infection, or may extend into larger venous trunks, and is then due to the spread of the infection along the vein walls (phlebitis). The thrombosis of the femoral vein during the puerperium or of a cerebral sinus following mastoid disease are typical examples of infective thrombosis.

(5) **SLOWING OF THE BLOOD STREAM—SPONTANEOUS OR POST-OPERATIVE THROMBOSIS. PULMONARY EMBOLISM.** Spontaneous thrombosis may occur under a variety of conditions, and in practically any vein in the body. Thrombosis, particularly of the veins of the lower limbs, not infrequently follows operations upon the abdominal or pelvic organs. When it occurs under these circumstances it is always a cause of anxiety to the surgeon because of the danger of the clot becoming detached and carried to the lung where it may block a branch of the pulmonary artery (pulmonary embolus). Infection is frequently blamed, but in most cases no evidence for this can be found. Also, the point where the thrombus forms—usually in the femoral vein—lies at a distance from the field of operation and is separated from it by a considerable extent of healthy tissue. This precludes direct spread either of infection or of thrombus formation from the site of the wounded tissues.⁵ Furthermore, thrombosis

⁵ The left femoral vein is more frequently involved than the right, and this has been explained by the greater resistance which the left common iliac vein offers to the blood flow in consequence of certain anatomical peculiarities. The left common iliac vein is longer and more oblique than the right and passes beneath the right common iliac artery. An adhesive band also in a certain proportion of cases passes between the anterior and posterior walls of the left vein. The vein of this side also, it is thought, suffers from pressure by a distended rectum or sigmoid flexure.

of this type is much more common now than in the past when aseptic technique was less perfect. We must therefore look elsewhere for the cause of post-operative thrombosis. The possible mechanisms concerned may be grouped under the following headings.

(a) *Slowing of the blood stream* as a result of enfeebled heart action, prolonged confinement to bed, debilitating diseases associated with a low metabolic rate and hypotension, or immobility of the limbs, seems to be an important factor in causation (p. 147).

(b) *Blood changes.* The platelets are increased after operations, and these elements show a greater tendency than is normal to clump together. The greater stickiness is due, according to Wright, to newly formed cells discharged from the bone marrow. The fibrinogen also is increased and, as a result of this, the rate of sedimentation of the corpuscles is hastened (p. 50).

(c) *The coagulation time* is shortened for the first few days after operation but it is doubtful whether an altered relationship between the different factors concerned in the clotting mechanism itself is really of importance in the production of post-operative thrombosis. At first sight the liberation of thromboplastin from the damaged tissues would seem to be the obvious cause of the thrombosis. Yet if this were responsible one would expect that thromboses would occur immediately following operation and not as is actually the case a week or ten days later. Moreover, thrombi composed of masses of platelets have been induced in animals whose blood had been rendered incoagulable, and post-operative thrombosis may occur in subjects whose blood shows a clotting time within the normal range.

Aschoff has made an experimental study of post-operative thrombosis and gives an interesting and logical explanation of the processes involved. He states that when the vein is completely obstructed, as is usual, the thrombus has a white portion or head which is directed proximally and a dark red portion or tail. If the flow of blood is not completely blocked the thrombus consists of the white portion alone. A minute examination reveals a framework of ribs or beams extending from the wall of the vein and traversing the entire substance of the white thrombus. The ribs are made up chiefly of massed platelets covered with a layer of leucocytes. *There is little or no sign of fibrin or of red cells so that this white plug is not a clot in the ordinary sense.* The longer red portion or tail of the thrombus extends distally for a variable distance along the vessel and is made up of all the elements of the blood in their normal proportions. Fibrin threads are plentiful. This portion is evidently formed by the coagulation of the blood en masse, as it is finally brought to a standstill by the obstruction of the vessel by the white thrombus, which is formed *while the blood is flowing*. The arrangement of the platelets to form the framework of the head of the thrombus is explained simply by the slowing of the blood current. The ribs or beams formed of accumulated platelets commence as low ridges upon the inner surface of the vein wall.

The mode of deposition is compared to the manner in which sand, though kept in suspension in a rapid stream, is deposited in a ribbed pattern upon the sea shore or at a river's mouth where the current is slowed. Though the flow of blood in the veins is continuous it is not absolutely even; eddies occur in the venous current and even slight muscular movement causes a certain irregular wave-like motion of the blood column which accounts for the deposition of the platelets, not in a continuous even layer but, in ripples. Also, owing to their lower specific gravity the platelets leave the axis or core of the stream and separating from the other blood elements come to occupy the more slowly moving zone next the vessel wall. Finally, it is the reduction of the velocity in this outer zone of the current to a certain critical level that causes the platelets to settle upon the vascular walls. The ribs or ridges increase in height by the aggregation of fresh platelet masses, and secondary ridges are later formed upon the primary ones until at last the fabric extends like a coral growth into the axis of the stream. The blood flows sluggishly through the sponge-like texture of the developing white thrombus, and by its pressure warps the beams in the direction of its flow. The leucocytes also because they have a lower specific gravity than the red cells, separate from these and move in the outer currents of the many streams into which the original blood column has been now divided. They cling to, and finally come to rest upon the walls of the new-formed channels, and ultimately filling them cause complete blockage of the vessel.

Between the white and red portions of the thrombus an intermediate portion or neck can often be seen. Here masses of red cells are also held in the white net though there is still a disproportionately large quantity of the white elements. Evidently the red cells had been caught in the mesh at the moment that the spaces in the forward part of the white thrombus had become filled with white cells and so brought the circulation to a standstill. The disposition in this way of the colored and colorless cells gives a stratified appearance to this intermediate part of the thrombus.

In the auricles during auricular fibrillation, in the slowing of the stream caused by a local dilatation of the blood channels, e.g., in an aneurysm or varicose vein, and wherever eddies are produced, a white thrombus either with or without a covering of clotted blood, is likely to form as a result of platelet deposition. The formation of such a thrombus in the femoral vein would perhaps be of little consequence if there were no danger of the plug of blood becoming detached, since the circulation would be carried on through collateral channels—or the thrombus itself would probably in time undergo canalization with consequent re-establishment of the current in the vessel. The grave danger as already mentioned is the transportation of the clot to the lungs and the obstruction of one or both branches of the pulmonary artery. Emboli found in this situation after death have the structure of a thrombus as described above, and are of a size which can be ac-

counted for only by their formation in a vessel such as the femoral. These facts indicate that a cramped or dependent position of the limbs, complete immobility or any other circumstances that will enhance or cause retardation of the circulation in the veins of these parts, quite apart from infection or vessel injury, will be conducive to thrombus formation.

The observations of Sandison are pertinent to the question of thrombus formation. Examining the blood flow through the capillaries of the rabbit's ear by the transparent chamber method, he observed thrombi in the process of formation. When the blood flow was retarded platelets were seen to cling to the wall of the capillary or venule. By the deposition of successive layers, a white thrombus was formed which as it grew extended a considerable way along the blood channels. A small proportion of leucocytes were included in the mass, but no erythrocytes.

Though slowing of the venous flow is probably the most important factor in the production of post-operative thrombosis, alterations in the blood itself which follow tissue injury, namely, the increase in the

number of platelets and their tendency to clump together, the rise in fibrinogen concentration and the effect of this upon the sinking rate of the cells, no doubt encourage the formation of the white thrombus. Anhydremia by increasing the viscosity of the blood also favors its occurrence.

The following are the chief measures employed in attempts to prevent post-operative thrombosis.

(1) Early movement of the limbs, to favor the venous flow.

(2) Avoidance of any restriction to respiration—which is an important factor in aiding the venous return from the limbs.

(3) Thyroid extract administration, to raise the metabolism and increase the circulation rate.

(4) Plenty of fluids, to prevent dehydration, and a diet composed largely of carbohydrate since the platelet count and the fibrinogen are raised by a high protein diet.

(5) The use of anticoagulants such as heparin by continuous administration (p. 89) and of sodium thiosulphate is in the trial stage.

CHAPTER XIII

THE MECHANISMS REGULATING THE REACTION OF THE BODY FLUIDS

PHYSICO-CHEMICAL PRINCIPLES

THE ELECTROLYTIC DISSOCIATION THEORY

When certain chemical substances such as acetic acid, hydrochloric acid and many others, are dissolved in water a proportion of their molecules—the proportion varies with the particular substance—undergo dissociation into their constituent *ions*. The latter move through the solution in all directions, some collide with one another and recombine, while a corresponding number are produced by the dissociation of other molecules. By the junction of some ions and the separation of others, the balance between undissociated (unionized) and dissociated (ionized) molecules is kept constant. That is, equilibrium is established. Substances whose molecules are dissociated in this way are known as *electrolytes*. An ion is an electrically charged atom or group of atoms and is referred to as a *cation* or an *anion* respectively according to the nature of the charge—positive or negative—which it holds. Cations are denoted by a plus sign or simply by a dot placed above the atomic symbol. The negative ion (anion) is indicated by a minus sign or an oblique dash. Thus HCl dissociates into the ions H^+ and Cl^- ; H_2O itself into H^+ and OH^- into H^+ and HCO_3^- . If an electric current be passed through the solution each ion carries a charge of electricity to one or other electrode, the anions (negative ions) migrating to the positive electrode or anode and the cations (positive ions) to the cathode. The conduction of an electric current through the solution will therefore be influenced by the concentrations of ions in the solution (i.e., upon the degree of dissociation of the particular electrolyte). Solutions of such substances as sodium chloride are good conductors, while solutions of others like cane sugar which undergo little or no dissociation are not much better conductors than pure water.

When (1) the degree of dissociation of an acid or other electrolyte and (2) the total concentration of the acid in the solution are known, then the concentrations of dissociated and undissociated molecules can be calculated. It is found that after equilibrium has been established the product of the concentrations of ions divided by the concentration of the undissociated molecules gives, at a given temperature and for a given electrolyte, a constant value which is known as the *ionization* or *dissociation constant*. This represents the operation of the mass law¹ as applied to the dissocia-

tion of electrolytes. So if HA represents an acid which is dissociated into cations H^+ and anions A^- then K_a represents the dissociation constant of the acid. The brackets enclosing the letters represent molar concentrations. Thus

$$\frac{\text{Dissociated}}{[\text{H}^+] \times [\text{A}^-]} \div \frac{\text{Undissociated}}{[\text{HA}]} = K_a \text{ (Ionization or dissociation constant)}$$

After equilibrium has been reached the velocity at which the molecules HA dissociate into H^+ and A^- is equal to that at which the latter combine to form HA. In this way an equilibrium between dissociated and undissociated molecules is maintained; thus, $HA \rightleftharpoons H^+ + A^-$. For weak electrolytes the degree of dissociation increases with dilution, so that at infinite dilution the dissociation is complete. The greater the degree of dissociation the higher will be the numerator of the equation, and the higher consequently will be the value of the dissociation constant.

HYDROGEN ION AND HYDROXYL ION CONCENTRATIONS

The ionization of acids

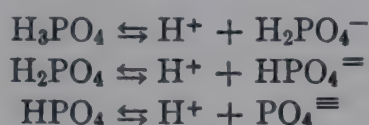
If a measured amount of a normal solution of acetic acid be titrated against a normal solution of sodium hydroxide a definite amount of the base will be required for neutralization. If the same quantity of a normal solution of HCl be taken and titrated as before, it will be found that precisely the same amount of base will be required for complete neutralization. From this it might be assumed that the two acids are equally strong. But it is known that at similar concentrations the acid properties of hydrochloric are incomparably greater than those of acetic acid. The former inverts cane sugar more powerfully, it tastes more acid, it has a greater destructive effect upon animal tissues, and it will displace acetic acid from its salts.

Hydrochloric acid is dissociated into hydrogen ions and chlorine ions. To the H-ion it owes its

¹ The mass law states that the velocity of a chemical reaction is proportional to the concentrations of the reacting substances. This law while it holds for dilute

solutions of such weak electrolytes as are present in blood is inaccurate in the case of strong electrolytes in concentrated solutions.

acid properties; it is the hydrogen *ion* concentration and not the total number of hydrogen atoms in its molecule that is responsible for the acid characters of any acid. The greater the degree of dissociation of the acid, the greater is the number of H-ion which it will yield in solution, i.e., the greater will be the H-ion concentration, and the greater consequently will be its acid nature. Thus HCl though it contains only one atom of hydrogen in its molecule undergoes almost complete dissociation and is in consequence a much stronger acid than carbonic (H_2CO_3) whose molecule contains two hydrogen atoms but dissociates to a very small extent into H^+ and HCO_3^- ; carbonic acid dissociates in two stages. Phosphoric is another weak acid which contains three atoms of hydrogen. It dissociates, however, to a greater extent than carbonic acid and in three stages:



The greater the degree of dissociation of an acid the higher will be the value of its dissociation constant. The latter therefore is a true measure of "acid properties." The dissociation constant of a very weak acid such as carbonic is only 0.0000003 (first stage); the first dissociation constant of phosphoric acid is 0.011.

The ionization of bases

The OH ion on the other hand gives to bases in aqueous solution their characteristic properties, and when a base and acid neutralize one another it is the union of the hydrogen ion of the acid with the hydroxyl ion of the base with the formation of a molecule of water that brings about neutralization, thus:



The ionization of a base may therefore be represented by an equation analogous to that given for an acid. Thus:

$$\frac{\text{Dissociated}}{[\text{B}^+] \times [\text{OH}^-]} = K_b$$

Undissociated
[BOH]

If the hydrogen ions are in excess the solution is acid; if the hydroxyl ions are in greater concentration the solution is alkaline.

The ionization of water—The reaction of a solution expressed in terms of hydrogen ion concentration

The dissociation of water may be represented by the equation

$$\frac{[\text{H}^+] \times [\text{OH}^-]}{[\text{H}_2\text{O}]} = K_w$$

Pure water has a definite though very slight conductivity value. The concentration of the molecules that are dissociated into H^+ and OH^- as compared with those undissociated is almost infinitesimal; the concentration of the H^+ and OH^- is so small that their presence produces no measurable decrease in the concentration of the total water molecules. The equation then may be written simply—

$$[\text{H}^+] \times [\text{OH}^-] = K_w$$

K_w , the dissociation constant for water therefore represents the product of these ionic concentrations and amounts to no more than 0.00000000000001.

Expressed more briefly, though perhaps more cryptically the value is 1×10^{-14} . The symbol -14 to the right of the figure 10 is termed the negative exponent or index, and means that in order to express the value in the form of a decimal fraction, as in the preceding paragraph the figure 1 must be placed 14 places to the right of the decimal point. Expressed as a vulgar fraction 10^{-14} would be $\frac{1}{100000000000000}$

Other examples of this system of notation are

$$\begin{aligned}10^{-1} &\text{ means } 0.1 \text{ or } \frac{1}{10} \\ 10^{-2} &\text{ means } 0.01 \text{ or } \frac{1}{100} \\ 10^{-3} &\text{ means } 0.001 \text{ or } \frac{1}{1000} \text{ and so on.}\end{aligned}$$

We already know that the H^+ and OH^- must be present in equal concentration and that the dissociation constant 1×10^{-14} is the product of these concentrations, i.e., the square of either. Therefore the square root of 1×10^{-14} i.e. 1×10^{-7} indicates the concentration either of the H^+ or of the OH^- .

The *actual weight* of ionized water in 1000 cc. (1 liter) of water is therefore

$$\begin{aligned}&1 \times 10^{-7} \text{ grams H ions (atomic weight of} \\ &\quad \text{hydrogen} = 1) \\ &17 \times 10^{-7} \text{ grams OH ions (atomic weight} \\ &\quad \text{of oxygen} = 16) \\ &\hline &\text{Total } 18 \times 10^{-7} \text{ grams ionized H}_2\text{O.}\end{aligned}$$

A solution containing 1 gram of hydrogen ion per liter is known as one having a normal concentration of hydrogen ions. Seventeen grams of OH ions in the same quantity of fluid is known as a normal solution of hydroxyl ions. Water is therefore 10^{-7} normal in both H^+ and OH^- ions. Since both are in equal numbers per unit of fluid, water is neutral in reaction.

If hydrochloric acid be added to water it is dissociated to the extent of over 90 per cent into H^+ and Cl^- . The concentration of H^+ in the water will therefore be greatly increased by the addition of acid. But it has already been seen that the product of the concentration of H^+ and OH^- in water is constant (K_w). This statement applies not only to pure water but to all aqueous solutions. *This is a fundamental fact* and upon it the determinations of the hydrogen ion concentration and the notations used for its expression are based. When therefore the H^+ are increased the OH^- must undergo a reciprocal reduction. If, for instance, the H^+ concentration is increased above its value in pure water, that is from 1×10^{-7} to say 1×10^{-6} (0.0000001 N to 0.000001 N) then the concentration of OH^- must undergo a reduction to 1×10^{-8} in order that the product of these two shall remain the same ($1 \times 10^{-6} \times 1 \times 10^{-8} = 1 \times 10^{-14}$). On the other hand if a base be added to water and the OH^- concentration increased from its value in pure water, i.e., from 1×10^{-7} to, let us say, 1×10^{-6} , the H^+ concentration must undergo a corresponding diminution from 1×10^{-7} to 1×10^{-8} (0.0000001 N to 0.00000001 N). It is clear therefore that all that is required in order to indicate the concentrations of both H^+ and OH^- ions is an expression which denotes the concentration of either one. The concentration of the H^+ has therefore been chosen to express the reaction of a solution. The term "hydrogen ion concentration" is abbreviated to the symbol cH. If the hydrogen ion concentration (cH) is greater than that of pure water the reaction is acid, if less than this value the reaction is alkaline, and if precisely the same the reaction is neutral. Thus:

If cH equals that of pure water i.e. 1×10^{-7} the reaction is neutral.

If cH exceeds that of pure water e.g. from 1×10^{-7} to 1×10^{-1} the reaction is acid.

If cH is less than that of pure water e.g. from 1×10^{-7} to 1×10^{-14} the reaction is alkaline.

The values represent the H^+ concentrations in terms of a normal solution (i.e., one containing 1 gram of ionized hydrogen per liter). No matter how concentrated in a solution the H^+ may be,

some OH^- are always present, and vice versa, with maximum alkalinity there are always present a small number of H^+ .

The symbol pH

The values of the hydrogen ion concentration as indicated above was found inconvenient. When the cH was 1×10^{-6} , 1×10^{-8} etc., the first factor could, for the sake of simplicity, be omitted. The expression then became cH, 10^{-6} , etc. But when the first factor was other than unity, e.g., as in 5×10^{-6} or 1.3×10^{-7} or 4×10^{-8} this obviously could not be done. The writing of such expressions became cumbersome and the hydrogen ion concentrations which they represented were difficult to keep in mind.

Sorensen in 1909 introduced a system of notation by which the negative exponent of the common logarithm (i.e., to the base 10) of the decimal fraction expressing the H-ion concentration, is employed as a positive number. For example the H-ion concentration of serum is 0.0000004 normal. The cH might be expressed either as 4×10^{-8} N, or as $1 \times 10^{-7.40}$ N. The latter expression is simplified by omitting the 10 and replacing the minus sign of the negative exponent by the symbol pH (hydrogen ion exponent). The value 7.40 is derived as follows. The log of the figure in the cH expression above, i.e., 4, is 0.6021 (cf. log tables). This log subtracted from the negative exponent, i.e., 8, gives the required figure 7.40. Similarly a solution 0.0000005 normal in H-ions may be expressed either as cH 5×10^{-8} or as cH $1 \times 10^{-5.3}$. The log of 5 is 0.6990; the pH is, therefore, $6 - 0.6990 = 5.3$.

In order to convert pH into cH the figure for the former is subtracted from the next higher whole number. The antilog of the difference is then obtained from the antilog table. This gives the first figure in the cH expression. The whole number gives the negative exponent of 10. For example, in the last expression given above (pH 5.3) the next higher whole number is 6; $6 - 5.3 = 0.7$. The antilog of 0.7 is 5; so the cH is 5×10^6 .

It must be remembered that a rise or fall in the pH indicates a change in hydrogen ion concentration (cH) in the opposite direction. Thus a pH of 5.00 indicates a higher acidity than a pH of 6.00. pH 7.00 of course indicates neutrality. Attention should be drawn to another point that is not quite so obvious, namely that a solution of a pH 5.00 is more acid not simply by a sixth than a solution of pH 6.00, but is in fact ten times more acid.

A pH of 3.00 represents an acidity 1000 times greater than a pH of 6.00. Similarly a solution of pH 11.00 is 1000 times more alkaline than one of pH 8.00. Recalling the decimal fraction which these figures represent will make this clear. Thus pH 5.00 = 0.00001 normal and pH 6.00 = 0.000001 normal.

BUFFERS

These are substances which when present in a solution maintain the latter at a relatively constant pH when an acid or alkali is added to it. That is, a buffer has the power to "soak up" or "tampon" the acid or base; it takes up the shock so to speak of the strong acid or base, hence the term buffer. A buffer or buffer system consists

The hydrogen ion concentration of the solution is equal to the product of the dissociation constant of the acid (K) and the ratio of the buffer pair. Thus:

Hydrogen ion concentration [H] = $K \frac{[HA]}{[BA]}$

In order to express the H ion concentration in terms of pH, the value for K is converted by means of logarithms to the corresponding pK figure. The equation then becomes:

$pH = pK + \log \frac{[BA]}{[HA]}$

This is known as the Henderson-Hasselbalch equation.

TABLE 12

HCl ADDED	$\frac{H_2CO_3}{NaHCO_3}$	[H]	[OH]	RELATIVE ACIDITY	RELATIVE ALKALINITY
grams					
0	2.27:11.9	0.000000057 N	0.000000176 N	0.57	1.76
10	2.27:11.5	0.000000059	0.000000170	0.59	1.70
50	2.27:10.0	0.000000068	0.000000142	0.68	1.47
100	2.27: 8.2	0.000000083	0.000000120	0.83	1.20
150	2.27: 6.3	0.000000108	0.000000093	1.08	0.93
200	2.27: 4.4	0.000000154	0.000000065	1.54	0.65
250	2.27: 2.6	0.00000026	0.000000039	2.6	0.39
300	2.27:0.68	0.0000010	0.000000010	10	0.10
310	2.27:0.31	0.0000022	0.0000000045	22	0.045
318	∞	0.00026	0.00000000039	260	0.0039
320	—	0.00045	0.00000000022	450	0.0022
330	—	0.0027	0.000000000037	2700	0.00037

of two parts—a weak acid and one of the salts of that acid. Acetic acid and sodium acetate; carbonic acid and sodium bicarbonate; phosphoric acid and sodium phosphate, are a few examples of such buffer pairs. Solutions of buffers are used in physiological experiments when for any reason it is desired to maintain the fluid medium at a constant hydrogen ion concentration, as for example in the study of the action of ferments.

The hydrogen ion concentration of a buffer solution is proportional to the ratio of the concentration of the free acid to the concentration of acid bound with alkali. The ratio of the buffer pair may be expressed as follows:

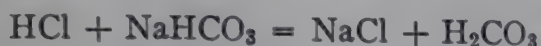
$$\frac{\text{Concentration of free acid}}{\text{Concentration of bound acid}} = \frac{[HA]}{[BA]}$$

The effect of a buffer in preventing changes in reaction of a solution when acid is added may be illustrated by an example given by L. J. Henderson (table 12).

One hundred liters of a 1 per cent solution of sodium bicarbonate is made up and kept in contact with an unlimited atmosphere containing 0.1 per cent of carbon dioxide. Time is allowed for the solution to absorb CO₂ and for equilibrium to be established between the pressure of gas in the atmosphere and that in the fluid. The temperature is kept constant at 17°C. The solution to start with is slightly alkaline. Hydrochloric acid is added in successive amounts up to 330 grams. It may be seen from the accompanying table that the reaction of the solution is practically neutral after as much as 150 grams of HCl have been added. Even after the addition of 250 grams the H-ion concentration is no more than 2.6 times that

of a neutral solution. It is not until the bicarbonate has been completely used up that the acid exerts any great effect. The ratio $\frac{H_2CO_3}{NaHCO_3}$ remains practically unchanged until some 50 grams of HCl have been added.

The reaction may be expressed as follows:



In this reaction three things have occurred.

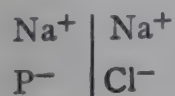
(1) The very strong acid, hydrochloric, has disappeared, the very weak acid, carbonic, having taken its place.

(2) The weak carbonic acid is volatile and is quickly got rid of by diffusion into the atmosphere. This continues until equilibrium between the pressure of gas in the atmosphere and that in the solution has been re-established.

(3) The bicarbonate has served as a reserve of base which has soaked up or buffered the added acid. The bicarbonate has of course been reduced and finally completely used up in the process.

THE DONNAN THEORY OF MEMBRANE EQUILIBRIUM

The Donnan effect is a state of ionic equilibrium set up between two sides of a membrane by the presence in a solution of electrolytes of an ion (such as protein) to which the membrane is impermeable. It is explained best by an illustrative example. Let two electrolytes, Na^+Cl^- and Na^+P^- , be separated by a membrane which is permeable to the ions Na^+ and Cl^- but impermeable to P^- . Thus,



When equilibrium has become established the product of the concentrations of the diffusible ions (Na^+ and Cl^-) on one side of the membrane equals the product of the concentration of these ions on the other side.

$$\begin{array}{c} [Na^+] \times [Cl^-] = [Na^+] \times [Cl^-] \\ | \\ [P^-] \end{array}$$

Also on either side of the membrane the total concentration of anions (whether diffusible or non-diffusible) is equal to the concentration of cations, for there is electrical neutrality.

$$[Na^+] = [P^-] + [Cl^-] \quad | \quad [Na^+] = [Cl^-]$$

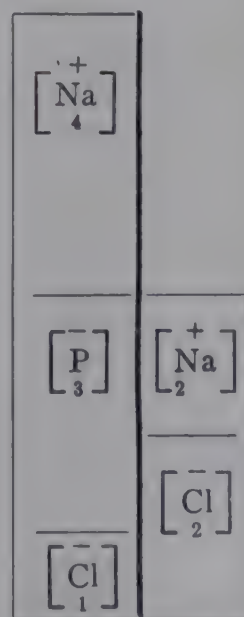
Since the anion P^- is non-diffusible it follows that the diffusible ions Na^+ and Cl^- must be unequally distributed on the two sides of the membrane. In other words, the non-diffusible ion hinders through electrostatic attraction the free diffusion of the oppositely charged Na^+ ions. The concentration of the Cl^- ion is therefore less and that of the Na^+ ion greater on the side occupied by the non-diffusible ion, thus:

$$\begin{array}{c} | \\ [Cl^-] < [Cl^-] \\ | \\ [Na^+] > [Na^+] \\ | \\ [P^-] \end{array}$$

The ratio of the Na^+ concentrations on the two sides of the membrane (which may conveniently be styled *right* and *left*) is the same as, but reciprocal to, the ratio of the Cl^- concentrations. Thus:

$$\frac{[Na^+ \text{ left}]}{[Na^+ \text{ right}]} = \frac{[Cl^- \text{ right}]}{[Cl^- \text{ left}]}$$

A potential difference is created between the solutions on the two sides of the membrane which is proportional to the logarithm of this ratio. When the ratio is 1:10 the potential difference at 19°C. amounts to 58 millivolts. The state of ionic equilibrium may be represented graphically, thus:



Numbers indicate concentrations in arbitrary units

The Donnan equilibrium is responsible for many physico-chemical effects of the utmost physiological importance, e.g., a difference of pH on two sides of a cell membrane across which H ions can diffuse, differences of electrical potential between

two sides of a membrane and differences in osmotic pressure between the interior of a cell and the extracellular fluids. (See also p. 340.)

THE REGULATION OF THE ACID-BASE EQUILIBRIUM OF THE BLOOD

Acids such as phosphoric, sulphuric and hydrochloric, carbonic and lactic as well as certain organic acids are continually being formed in the processes of metabolism. In diseased conditions, e.g., diabetes, acids such as β -hydroxybutyric and aceto-acetic acids are produced in excessive amounts. Yet in health the reaction of the blood remains remarkably constant at about pH 7.4, and even in disease may show little or no variation from the normal, for the adjusting mechanisms which are called into play to neutralize and remove excess acid perform their duties with extraordinary efficiency.

The reaction of the blood is protected by three lines of defense.

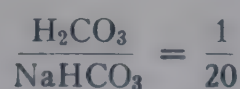
- (1) The buffer systems of the blood
- (2) Excretion of carbon dioxide by the lung
- (3) Excretion of fixed acids by the kidney

The intestinal mucosa also assists to some extent in the removal of acid, particularly of a part of the phosphoric. The rôle played by the kidneys in the regulation of the acid-base balance is considered in chapter XXXVI.

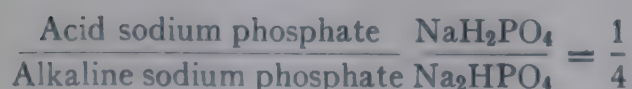
THE BUFFER SYSTEMS OF THE BLOOD may now be enumerated.

I. In the plasma (primary buffers):

- (1) Carbonic acid (free acid) and acid bound as sodium bicarbonate. Ratio 1 to 20.

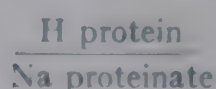


- (2) The acid and alkaline phosphates of sodium. Ratio 1 to 5.



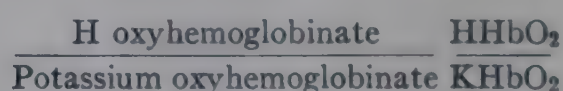
NaH_2PO_4 may be regarded as a weak acid and Na_2HPO_4 as the salt of the buffer pair.

- (3) Plasma proteins which at the reaction of the blood behave as acids and so combine with base (p. 540).

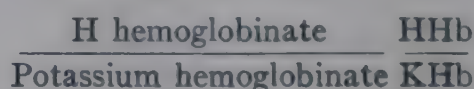


II. In the corpuscles (secondary buffers). It is to be remembered that whole blood consists of two liquid phases separated from one another by the membrane of the corpuscles. Different materials in different concentrations exist within the red cell and in the plasma. The corpuscles as well as the plasma contain important buffers and an interchange of water, anions and H^+ occurs between the two across the membrane. The corpuscular membrane, on the other hand, is impermeable to the cations Na and K, and to the colloidal anions, hemoglobin and plasma protein. The buffers of the red cells are:

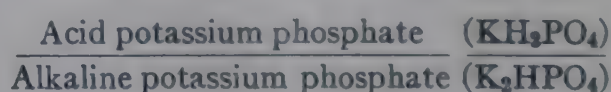
(1) Oxyhemoglobin and reduced hemoglobin act each as a weak acid of a buffer pair of which the potassium salt of the pigment acts as the other half. Thus:



and

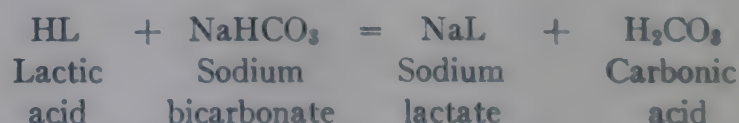


- (2) The potassium salts of phosphoric acid:



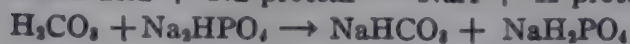
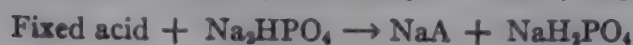
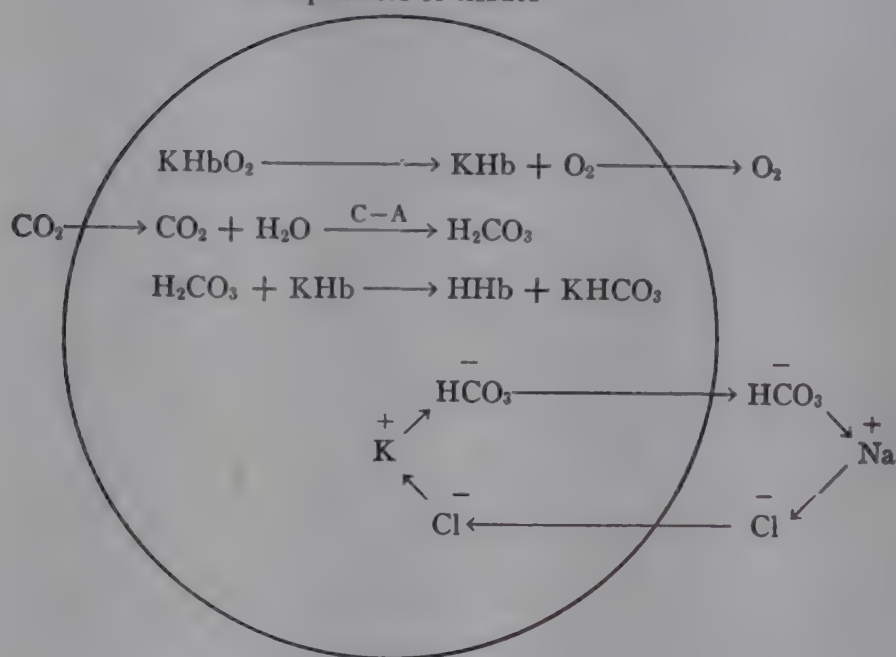
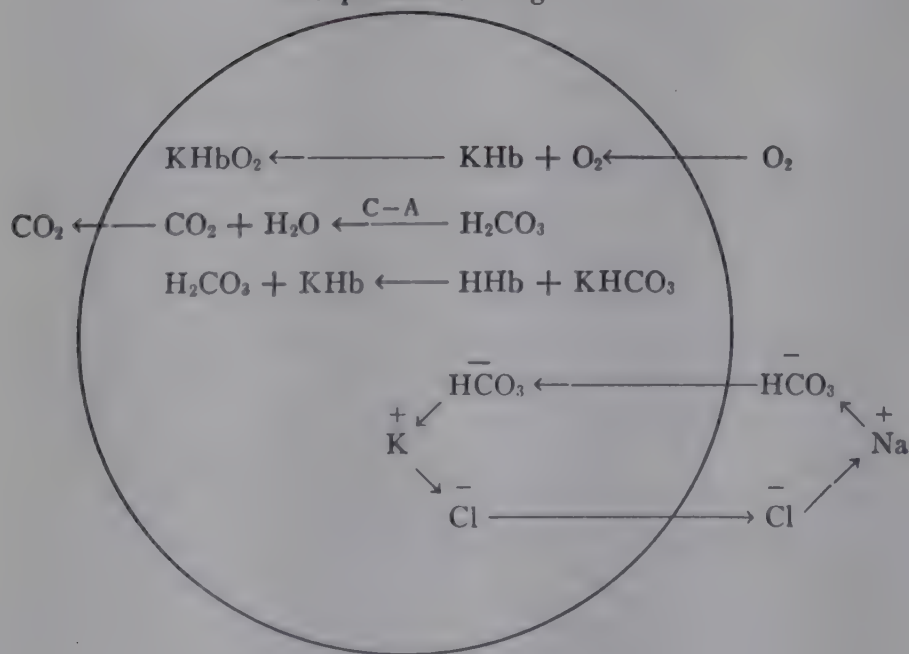
The reactions by which acids are buffered in the blood may now be considered in more detail. They may be grouped under the following heads:

(1) *Fixed acids* formed during metabolism, e.g., lactic, sulphuric, phosphoric, etc., are buffered by the bicarbonate in a way analogous to that already described on page 000. Taking lactic acid (HL) as a type the reaction may be expressed by the following equation:



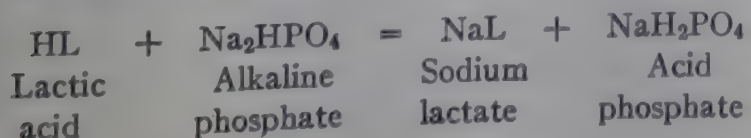
The comparatively strong fixed acid is thus replaced by a neutral salt. Phosphates, sulphates, lactates, etc., are excreted in the urine; lactic acid is also removed to a large extent through its conversion to glycogen in the liver and muscles. Carbonic acid is removed through the diffusion of CO_2 into the alveolar air. The great value of bicarbonate in maintaining neutrality of the body fluids is not due so much to its true buffering action, i.e., to the replacement of a strong by a weak acid but to the fact that the latter is volatile and can be eliminated by the lungs.

SCHEME TO ILLUSTRATE THE BUFFERS OF BLOOD

In plasma*Between red cells and plasma**In capillaries of tissues**In capillaries of lung*

C—A = carbonic anhydrase

Some of the fixed acid also reacts with the alkaline phosphate with the production of a salt of the acid and a greater proportion of acid phosphate.



The ratio $\text{NaH}_2\text{PO}_4/\text{Na}_2\text{HPO}_4$ is readjusted by the excretion of the excess acid phosphate in the urine. The phosphate mechanism for removal of excess acid from the body is much less efficient however than in the bicarbonate system, for the reasons that (a) the excretion by the kidney is

relatively slow, and (b) base is lost from the body in combination with the acid. Plasma protein also yields base to neutralize fixed acids.



(2) *Carbonic acid* which as a product of tissue activity is produced in much greater quantities (800 to 900 grams daily) than any other acid, is buffered mainly by base released from hemoglobin. When carbon dioxide enters the blood the sodium bicarbonate of the plasma increases. The increase occurs to a much less extent if plasma separated from the red cells is exposed in the same way to a high tension of CO_2 . The rise in the sodium bicarbonate of whole blood is the result of interchanges between corpuscles and plasma.

It was thought at one time (Zunz) that the rise in plasma bicarbonate was due to the passage of base from the corpuscles into the plasma. It was shown by Gürber and by Hamberger, however, that the rise of bicarbonate was accompanied by a reduction in chloride. It was concluded that chloride derived from the NaCl of the plasma diffused into the red cell and the base thereby released combined with carbonic acid to form bicarbonate. This mechanism is referred to as the "*chloride shift*." The interchanges between the corpuscles and plasma are believed to occur as follows. As the blood passes from the arterial to the venous side CO_2 is absorbed and diffuses into the red cell. Herein, through the action of an enzyme—*carbonic anhydrase*—, it is converted to carbonic acid (H_2CO_3). The oxyhemoglobin becomes at the same time reduced. Reduced hemoglobin is a much weaker acid than oxyhemoglobin and so gives up its alkali to the carbonic acid (see also p. 338). Bicarbonate (KHCO_3) and HHb are formed. The base which previously had been bound to the non-diffusible hemoglobin is now bound as bicarbonate. The concentration of bicarbonate ions (HCO_3^-) in the cells is thereby raised above that in the plasma and, as a result, this anion diffuses across the corpuscular membrane. Since the cations cannot diffuse, the ionic equilibrium between the plasma and the interior of the cell will tend to become disturbed. The balance is adjusted by the diffusion of Cl^- ions from the plasma into the corpuscle (Donnan effect) where they combine with base. The HCO_3^- ions which leave the cells combine with the sodium released from chloride to form plasma bicarbonate. (See schema below.)

The exchanges just described increase the concentration of osmotically active substances within

the cells; water therefore passes from plasma to corpuscle, which, as a result increases in volume. Though described in steps, the reactions actually occur simultaneously; in the lungs, where CO_2 leaves the blood, and hemoglobin becomes a much stronger acid as a result of oxygenation, they are reversed. The alkali is released from its combination with chloride and recombines with hemoglobin. The chloride passes out of the cell. The base furnished by hemoglobin thus serves as the chief means by which CO_2 is carried from the tissues to the lungs.

Carbonic acid is also buffered to a minor extent in the plasma through the protein and phosphate buffer systems. The plasma protein yields base and more free (acid) protein is produced. The alkaline phosphate is converted to the acid phosphate with a consequent fall in the $\text{Na}_2\text{HPO}_4/\text{NaH}_2\text{PO}_4$ ratio.

It is evident from the foregoing description of the interchanges between the corpuscles and the plasma that whole blood as compared with plasma possesses a much greater power to buffer CO_2 . For this reason plasma separated from the red cells without precautions to prevent the escape of CO_2 is called "separated plasma" to distinguish it from plasma of whole blood, i.e., plasma in contact with the red cells. Only when precautions have been taken to prevent the escape of CO_2 during the separation of plasma from the cells will the separated plasma have the same reaction and amount of bicarbonate as existed when it was in the body. Only then will the equilibrium between cells and plasma be maintained unchanged. Such plasma is therefore referred to as "true plasma" (see also p. 339).

ALKALI RESERVE—ACIDOSIS AND ALKALOSIS THE ALKALI RESERVE

This term was brought into use by Van Slyke and Cullen to denote the amount of base in the blood which is available for the neutralization of fixed acids, e.g., lactic, hydrochloric, etc. When CO_2 enters the blood, base is liberated in the manner already described and bicarbonate, NaHCO_3 , is formed in the plasma. The plasma bicarbonate then is a measure of the base left over after all acids stronger than H_2CO_3 have been neutralized and thus indicates the reserve of alkali readily available for the neutralization of such acids. The quantity of plasma bicarbonate therefore gives indirectly a measure of the extent of the production of fixed acids in the body. For if acid production be increased the bicarbonate

becomes reduced, its base being given up for the neutralization of the stronger acids. The term alkali reserve, it should be emphasized, refers only to base bound as bicarbonate and not to the total base of the blood. A large quantity of base, Na, K, Mg and Ca is already bound as salts of fixed acids, chiefly sodium chloride, which the weak acid H_2CO_3 is unable to displace (fig. 30). Though changes in the alkali reserve may result from alterations in the body's store of total base, they also occur quite independently of any such change, i.e., simply from variations in the distribution of base between carbonic acid and fixed acids.

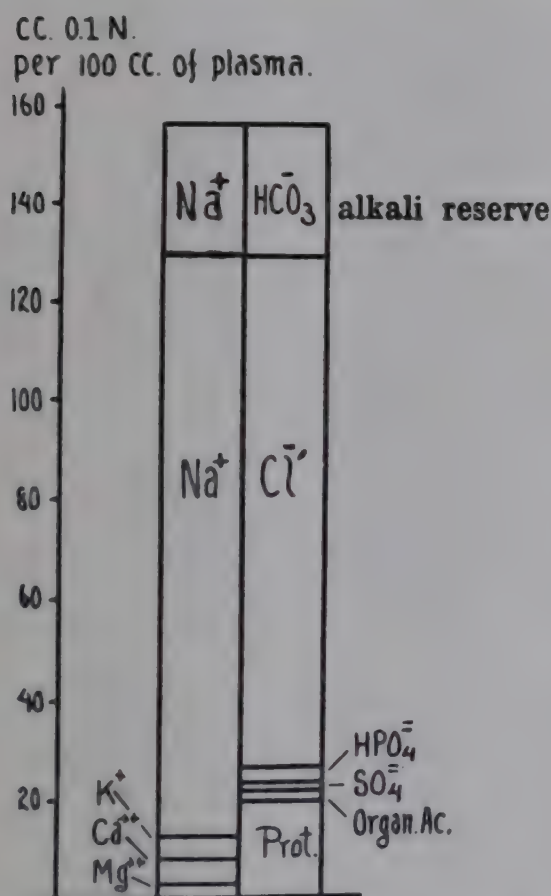


FIG. 30. Diagram illustrating normal acid-base balance (modified from Gamble, Ross and Tisdall).

It is also important to remember that the term alkali reserve refers to the *absolute* quantity of bound CO_2 in the plasma and has no reference to the ratio between this value and the quantity of the free CO_2 . Upon this ratio— $\text{H}_2\text{CO}_3/\text{NaHCO}_3$ —the pH of the plasma depends. The plasma bicarbonate may therefore be greatly depleted, yet if the free carbonic acid be reduced to a corresponding extent and the normal ratio of 1:20 thereby maintained, the hydrogen ion concentration will show no appreciable change. Large quantities of acid may be formed in the body yet such is the store of bicarbonate that these, as in the case of the example given on page 102, are taken care of and not until extreme depletion of the bicarbonate

buffer occurs does any great change in blood reaction result.

Rapid adjustments of the ratio $\text{H}_2\text{CO}_3/\text{NaHCO}_3$ are brought about through the exquisite sensitivity of the respiratory center to changes in pH, and to the chloride shift mechanism. The slightest reduction in plasma bicarbonate through its decomposition by acid is met by increased pulmonary ventilation and an equivalent reduction in the numerator of the above expression, i.e., by the elimination of CO_2 by the lungs. Low arterial and alveolar CO_2 tensions are therefore associated with a low alkali reserve.

On the other hand, when excess CO_2 is contained in the blood a compensatory increase in bicarbonate results (chloride shift). So high arterial and alveolar CO_2 tensions are associated with a high alkali reserve.

When excessive amounts of CO_2 are removed from the body (e.g., by forced breathing) a movement of chloride and bicarbonate ions occurs in the reverse direction; the plasma bicarbonate is reduced.

Measurement of the alkali reserve

The alkali reserve is measured by exposing a sample of plasma to an atmosphere of carbon dioxide under conditions similar to those existing in the body, and determining the volumes of gas which are combined as bicarbonate. This is spoken of as the *carbon dioxide combining power*, or the *carbon dioxide capacity* of the plasma. The determination is made as follows. Blood (15 cc.) is drawn from a vein into a syringe containing oxalate to prevent coagulation. Venous stasis, which would cause the accumulation of carbon dioxide and so increase the plasma bicarbonate through the chloride shift mechanism (p. 106) is avoided. The blood is then centrifuged under a layer of paraffin oil which prevents the escape of carbon dioxide, and so a reduction in plasma bicarbonate. After centrifuging the plasma is pipetted off, placed in a saturating vessel and equilibrated with air containing 5.5 per cent carbon dioxide, i.e., the percentage of carbon dioxide in normal alveolar air (tension 40 mm. Hg). The observer's own alveolar air is usually employed. He expires as deeply as possible after an ordinary inspiration into the saturator, through a bottle filled with glass beads; these condense the moisture from the breath, which would otherwise dilute the plasma sample. The saturator is turned end over end for a couple of minutes; the plasma is thus spread over the interior of the vessel in a thin film. After equilibration a measured amount of the plasma (3 cc.) is introduced into a Van Slyke gas apparatus (fig. 31). The CO_2 is then liberated by the action of an acid in the presence of a vacuum, and measured. The result gives the total carbon dioxide

content of the plasma. In order to obtain the quantity combined as bicarbonate the value for the dissolved carbon dioxide, obtained by calculation from the absorption coefficient of carbon dioxide, and the tension of the gas (40 mm. Hg) at which the sample was equilibrated (p. 338), is subtracted (p. 111). The normal values for the carbon dioxide combining power of plasma as so determined range from 53 to 75 volumes

and 75 volumes CO_2 per cent. The free CO_2 being one-twentieth of this, amounts therefore to from about 2.5 to 3.5 volumes per cent.

In disease the pH of the blood, unless in the terminal stage, e.g., diabetic coma, never becomes actually acid, i.e., reaches a pH below 7.0, and as just stated, a reduction in the alkali reserve may occur with little or no change in blood reaction. The limits of pH compatible with life are probably not higher or lower respectively than 7.8 and 6.8. A pH of the latter value has been observed in a case of diabetic coma which ultimately recovered under insulin treatment. The pH of venous blood during rest is lower by 0.02 than that of arterial blood. The red cells are more acid than the plasma by 0.08 to 0.14 pH.

ACIDOSIS AND ALKALOSIS—DEFINITIONS

Few terms in physiology have caused more confusion than these. "Acidosis" has been used with at least two different meanings. The term was originally introduced by Naunyn to denote the production in the body of the abnormal acid metabolites, β -hydroxybutyric and aceto-acetic acids.

The term was used later by Van Slyke and Cullen to mean simply a decrease in the alkali reserve (plasma bicarbonate) below the normal level. This is the sense in which the term has been usually employed. Since the bicarbonate represents the base in the blood which is left over after the non-volatile acids have been neutralized, a reduction in alkali reserve indicates frequently—though not necessarily—that an excess of fixed acids are being produced or retained in the body. We have seen how very efficient the compensatory mechanisms are in keeping the pH constant, and that an acidosis either in the sense of a reduction in alkali reserve or of an increased acid production may or may not be associated with a depression of the pH (reduced alkalinity). We also know that the term acidosis cannot mean any *real* acidity of the blood—a pH below 7.00—for this is incompatible with life, and only occurs when the alkali reserve is very greatly reduced and the bicarbonate buffer ratio cannot be maintained anywhere near the normal value. *Alkalosis* carries the corresponding meaning of an increased alkali reserve. This may or may not be associated with a rise in blood pH (i.e., increased alkalinity).

Van Slyke in a later paper recognizes nine possible acid-base states, one normal, and eight abnormal (fig. 32). He avoids the terms acidosis

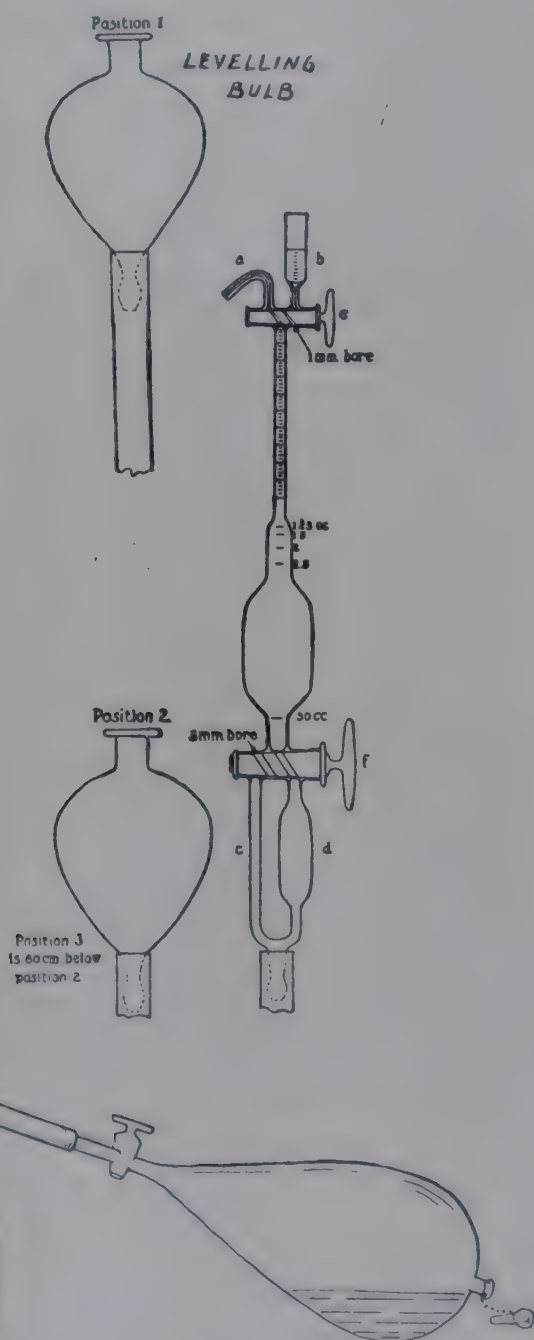


FIG. 31. Left hand figure (Van Slyke), volumetric blood gas apparatus; right hand figure apparatus for equilibrating plasma with alveolar air (modified from Peters and Van Slyke).

per cent. A reduction below 50 volumes or so would therefore constitute "acidosis"; above 75 volumes, "alkalosis."

THE NORMAL ACID-BASE BALANCE AND ITS VARIATIONS

The pH of the blood in health varies between 7.3 and 7.45. The normal value for the plasma bicarbonate of venous blood ranges between 53

and alkalosis, using the more precise designations, alkali deficit or CO_2 excess, and alkali excess or CO_2 deficit, respectively. In any one of these, the ratio $\text{H}_2\text{CO}_3/\text{NaHCO}_3$ may be either increased or diminished, with a consequent elevation or depression of pH; the acid-base condition is then said to be *uncompensated*. On the other hand, when adjustments occur to maintain the ratio at the normal value the condition is said to be *compensated*.

Uncompensated alkali excess. In this condition the $[\text{NaHCO}_3]$ is increased without a proportionate rise in

fore normal. A disturbance of this nature will result from conditions which cause (1) but of less severe degree (area 4).

Compensated CO_2 excess. $[\text{H}_2\text{CO}_3]$ increased but accompanied by a proportional rise in $[\text{NaHCO}_3]$; pH is normal. This state occurs in conditions in which there is retention of CO_2 , e.g., emphysema (area 4).

Normal acid-base balance. $[\text{H}_2\text{CO}_3]$, $[\text{NaHCO}_3]$ and pH are normal (area 5).

Compensated alkali deficit. $[\text{NaHCO}_3]$ is reduced and $[\text{H}_2\text{CO}_3]$ diminished proportionately; pH normal. The condition results from the abnormal production of fixed acids as in diabetes; acid retention as in nephritis; or

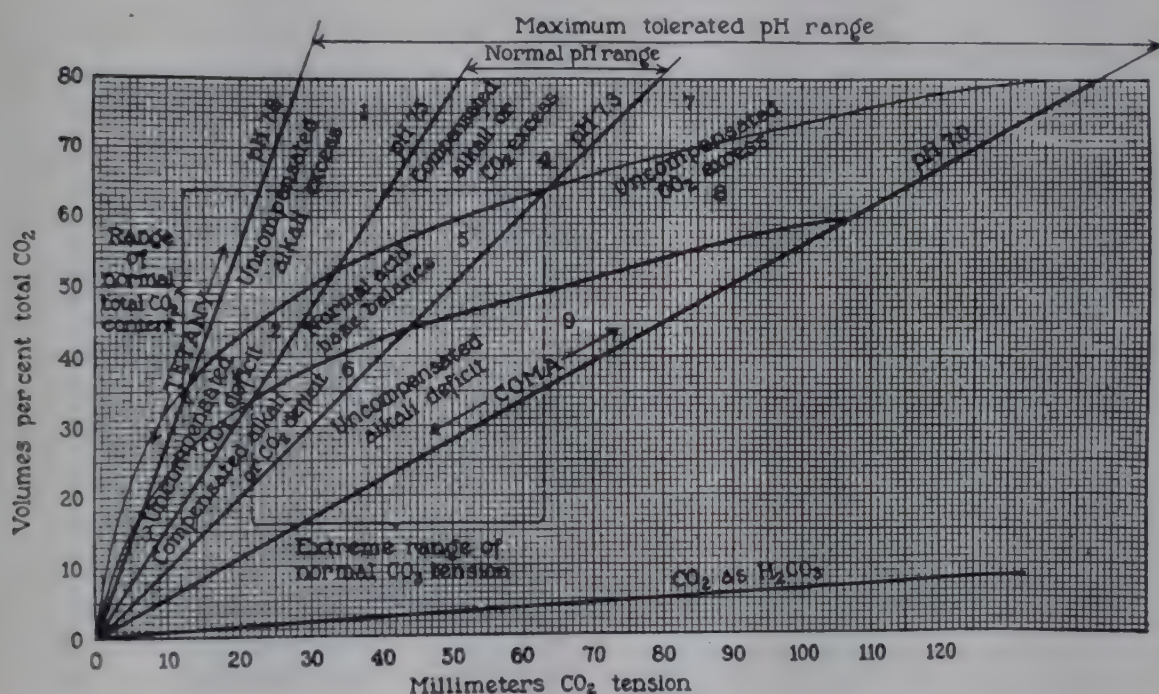


FIG. 32. Normal and abnormal variations of the $[\text{HCO}_3^-]$, $[\text{H}_2\text{CO}_3]$, CO_2 tension, and pH in oxygenated human whole blood drawn from resting subjects at sea-level.

The curved lines are the CO_2 dissociation curves (p. 338) of reduced (upper curve) and oxygenated blood (lower curve). The straight slanting lines indicate different $\text{NaHCO}_3/\text{H}_2\text{CO}_3$ ratios, the pH at each ratio having been calculated from the Henderson-Hasselbalch equation (p. 102). The CO_2 present as bicarbonate at any point is obtained by subtracting from the total CO_2 the relatively small amount present as H_2CO_3 , indicated by the line near the bottom of the chart. The ratio, and so the pH, is the same at all points along a given line. Thus, the intersection of the CO_2 dissociation curves by these so-called isohydronic lines marks off nine areas corresponding to the acid-base states described above (after Van Slyke).

$[\text{H}_2\text{CO}_3]$. The pH is raised (i.e., the alkalinity of the blood is increased). This may result from the ingestion of large quantities of alkali (sodium bicarbonate) or from the loss of HCl by vomiting as in pyloric obstruction (area 1, in figure 32).

Uncompensated CO_2 deficit. In this the $[\text{H}_2\text{CO}_3]$ is reduced below normal but the $[\text{NaHCO}_3]$ is not lowered to a corresponding extent. The pH is raised. A disturbance of this nature may result from forced breathing, or the hyperventilation induced by hot baths, high altitudes or shallow breathing (p. 365). It is sometimes also referred to as "gaseous alkalosis." Partial compensation occurs as evidenced by the reduced excretion of acid and ammonia in the urine and the increase in the urinary bicarbonate (areas 2 and 3).

Compensated alkali excess. The $[\text{NaHCO}_3]$ is raised but a parallel rise occurs in $[\text{H}_2\text{CO}_3]$. The pH is there-

from the ingestion of mineral acids or acid producing salts (CaCl_2 , NH_4Cl). This and (9) are the acid-base states to which the term "acidosis" has been usually applied. The compensatory adjustments are evident in the increased acid and ammonia excretion in the urine and the lowered CO_2 tension in the alveolar air. Alkali deficit may also result from the increased excretion of base as occurs in dehydrated states (p. 17) and in animals following the production of a pancreatic fistula (area 6).

Compensated CO_2 deficit. This is a reduction in $[\text{H}_2\text{CO}_3]$ and a parallel reduction in $[\text{NaHCO}_3]$. The pH is therefore normal. This state results from less severe grades of the conditions which cause (2) above. The excretion of NaHCO_3 by the kidney is much slower than the excretion of CO_2 by the lungs, so a condition

of CO_2 deficit which is uncompensated to start with, later tends to become compensated (area 6).

Uncompensated CO_2 excess. $[\text{H}_2\text{CO}_3]$ is increased but is not balanced by a proportional rise in $[\text{NaHCO}_3]$. The pH is lowered (i.e., blood is less alkaline). This is sometimes referred to as "gaseous acidosis." Such a state results from a hindrance to the excretion of CO_2 as may occur in pneumonia, obstruction to breathing or depression of the respiratory center by morphine. There is partial compensation, i.e., the bicarbonate is raised above the normal and there is an increased excretion of acid and ammonia by the kidneys (areas 7 and 8).

Uncompensated alkali deficit. $[\text{NaHCO}_3]$ is reduced without there being a parallel reduction in $[\text{H}_2\text{CO}_3]$. The pH is lowered (i.e., the blood becomes less alkaline). Such an acid-base state occurs when large quantities of fixed acids— β -hydroxybutyric and aceto-acetic—are produced as in diabetic coma and in the terminal stages of nephritis when acid excretion is greatly impaired. The plasma bicarbonate is severely depleted; the CO_2 combining power of the plasma may be less than 20 volumes per cent (area 9).

It will be evident after a consideration of some of the foregoing acid-base states that the terms "acidosis" and "alkalosis" if used to denote respectively a fall or a rise in plasma bicarbonate are misleading, since the blood may be no more acid or alkaline than normally. For example, in (2) above, the blowing off of CO_2 will result in a certain degree of compensatory reduction of NaHCO_3 . The reduction in the alkali reserve would therefore entitle it to be called acidosis though the blood was actually more alkaline than normally. In (8) on the other hand the blood is less alkaline than normally yet a certain degree of compensatory increase in the alkali reserve would have occurred. The term alkalosis would therefore apply, though its use would give an erroneous idea of the true state of the acid-base balance. On account of the ambiguity of these terms and the confusion which is likely to arise from their use it has been recommended by the British Medical Research Council that the term *acidemia* be used for a state in which the pH is lowered and that the term *acidosis* be restricted to indicate a lowered alkali reserve with unaltered pH. The term alkalosis would be retained as the corresponding term to indicate the reverse condition, namely an increase in the reserve alkalinity. The term *alkalemia* would indicate a blood state in which the pH was raised.

MEASUREMENT OF THE HYDROGEN ION CONCENTRATION OF THE BLOOD

(1) *Electrometric method*

(a) *By means of hydrogen electrodes.* Two hydrogen electrodes are employed. The method is

derived from the fact that in a suitable concentration cell a difference of potential between a metal electrode (e.g., zinc) and a solution of its ions (e.g., zinc sulphate) is set up which is proportional to the ion concentration. A hydrogen electrode, composed of platinum black saturated with hydrogen gas is therefore used to determine the hydrogen ion concentration of a solution. One of a pair of hydrogen electrodes is placed in a solution of known hydrogen ion concentration and the other in the unknown solution. When the two electrodes are connected an electromotive force is developed from which the hydrogen ion concentration may be calculated. Another electrometric method involves the use of quinhydrone—*quinhydrone electrode*. One platinum or gold electrode is placed in a solution of known hydrogen ion concentration; and the other dips into the unknown solution. A small quantity of quinhydrone is added to each solution. The quinhydrone undergoes oxidation to quinone or reduction to hydroquinone according to the hydrogen ion concentration of the solution. A potential difference is set up between the two electrodes and from its magnitude the H ion concentration is calculated.

(b) *By means of the glass electrode.* Within the last few years this method has come into very general use for pH determinations of biological materials. Like the hydrogen electrode the potential of the glass electrode, in an electrical system similar to that just described for the latter, varies with changes in pH. It is standardized against the hydrogen electrode. The glass electrode has the great advantage that it is unaffected by oxygen, protein content and other substances in the test material which interfere with the accuracy of other methods. Theories as to its action cannot be discussed here; the reader is referred to Dole's book, "Experimental and Theoretical Electrochemistry."

(2) *Colorimetric method*

In the method of Levy, Rowntree and Marriott as modified by Dale and Evans, the blood is placed without loss of CO_2 in a collodion sac and dialyzed for 15 minutes against a solution of normal saline. A few drops of 0.02 per cent of the indicator neutral red are added to the dialysate. The latter is then placed in a comparator and its color matched with that of a phosphate mixture of known pH and containing neutral red in the same concentration as the blood dialysate. The reader is referred to Dale and Evans' article for the details of the method.

It might be thought that the H ion concentration could be reduced through the dilution of the analyzed substance by the saline in the apparatus. But, since the pH of a buffered solution depends on the *ratio* of free to bound acid and this of course will not be altered, so, moderate dilution does not effect the result. In the colorimetric method of Cullen, the pH is determined directly (i.e., without dialysis) upon plasma which is diluted 20 times; phenol red is used as indicator. In this method a correction must be made for dilution and also for protein content.

(3) From the $H_2CO_3/NaHCO_3$ ratio

The total CO_2 in a sample of plasma is obtained as described on page 107. The free CO_2 , i.e., the CO_2 in simple solution, is obtained by calculation from the partial pressure of CO_2 with which the sample was equilibrated. The calculation is made as follows. The figure for the partial pressure of CO_2 is multiplied by the absorption coefficient of CO_2 in plasma, which at $38^\circ C$. is 0.510 (p. 314). If, then, the partial pressure of CO_2 is 40 mm. Hg

(as in normal arterial blood), the quantity of gas dissolved in 100 cc. of plasma is

$$40 \times \frac{100 \times 0.510^*}{760} = 2.68$$

The total CO_2 is, say, 56 volumes per cent. Then the combined CO_2 is $56 - 2.68 = 53.32$ volumes per cent.

The pH may now be calculated from the Henderson-Hasselbalch equation (pp. 102 and 337).

$$pH = pK_1 + \log \frac{[BHCO_3]}{H_2CO_3}$$

The value of pK_1 † for plasma is 6.10, therefore

$$pH = 6.10 + \log \frac{53.32}{2.68}$$

* $100 \times \frac{0.510}{760} = 0.0672$ is a constant factor by which the CO_2 partial pressure (in mm. Hg) is multiplied to give the volumes of dissolved CO_2 .

† K_1 includes the first dissociation constant of H_2CO_3 and a figure representing the dissociation of $NaHCO_3$ under the conditions existing in plasma.

SECTION II. THE CIRCULATION OF THE BLOOD

CHAPTER XIV

THE DYNAMICS OF THE CIRCULATION

GENERAL OUTLINE OF THE VASCULAR SYSTEM

The main anatomical features of the circulatory system may be very briefly recalled. The vessels constituting the vascular bed differ widely in their calibers in different regions and on the basis of their size, structure and physiological relationships are divisible into four main groups—the *arteries*, *arterioles*, *capillaries* and *veins*. The arteries are constructed to withstand a high pressure. Their walls are thick and contain a large proportion of elastic tissue and some involuntary muscle fibers, an outer sheath of connective tissue and an inner lining of endothelial cells. The outer coat is called the *tunica adventitia*, the middle coat the *tunica media* and the inner coat the *tunica intima*. The relative proportions of muscular and elastic tissues vary with the size of the artery. The largest vessels such as the aorta and the pulmonary artery, are relatively poor in muscular tissue but contain a large proportion of elastic fibers. The medium sized arteries contain a relatively large amount of muscle and less elastic tissue, while in the smaller vessels the muscle is greatly in excess. The walls of the arteries are supplied with minute vessels—*vasa vasorum*—which ramify in the outer and middle coats. They also are furnished with nerves. As the arterial system is traced peripherally the vessels are found to break up into innumerable branches whose calibers become reduced with successive divisions. Finally minute vessels—the *arterioles* are formed. These vary in size but on the average are about 0.2 mm. in their outside diameters. Their walls are relatively thick and composed almost entirely of smooth muscle lined by an endothelial layer and sheathed by a scanty adventitia. The muscle fibers are supplied with excitor and inhibitor nerves (p. 232). The arterioles after a course of variable length lose their muscular and connective tissue coats while the inner endothelial tubes that remain are continued on as extremely fine, hair-like vessels, the *capillaries*. The capillaries, a number of which arise from a single arteriole, are from 8 to 12 microns in diameter and about a millimeter long. Lying upon the outer surface of the capillary wall in amphibians and certain other cold-blooded vertebrates a scattering of peculiar cells with a number of long processes is to be seen. These are called after their discoverer, Rouget cells (see also p. 265). The processes of the neighboring Rouget cells join with one another to form a loose mesh-work which encloses the capillary. The capillaries form maze-like plexuses with one another and connect the arterial and venous systems. Their venous ends converge to form first the smaller *veins* or

venules. By the confluence of these to form larger channels, and the successive junctions of veins of ever increasing caliber, the blood is finally poured into the right auricle by two large trunks, the superior and inferior *venae cavae*.

The veins have much thinner walls than the arteries, but like these they possess three coats—intima, media and adventitia. The middle coat is only a fraction of the thickness of that of a corresponding artery. It is composed of a relatively small amount of unstriped muscle and a large amount of connective tissue: the elastic tissue is scanty. The outer coat of the vessel is disproportionately thick, being several times thicker than the tunica media. The valves which are present in some of the larger veins are formed by foldings of the tunica intima.

The course of the blood through the body from the left ventricle to the right auricle is spoken of as the *greater* or *systemic circulation*. From the right auricle the blood enters the right ventricle from which it is discharged into the pulmonary artery and thence through the *lesser* or *pulmonary circulation*. The heart serves as a two cylinder pump situated between these two systems. The left ventricle receives arterial blood from the lesser circulation, and drives it through the systemic vessels. The right ventricle is supplied with venous blood from the systemic vessels and pumps it through the pulmonary circuit. Both sides of the heart contract synchronously and obviously must eject the same quantity of blood in a given time. Otherwise blood would be dammed back in some part of the circulation.

THE PRINCIPLES GOVERNING THE FLOW OF A LIQUID THROUGH A SYSTEM OF TUBES

The vascular system may with advantage be considered here in its purely physical aspect, and its more physiological characters be left to be dealt with later. The movement of the blood within the vascular channels is governed by those physical laws which govern the flow of liquids in any other closed system of cylindrical tubes. For this reason the dynamics of the circulation may be more simply explained and the more readily appreciated from illustrations furnished by artificial models.

Figure 33 represents a model comprising a reservoir and a long horizontal tube from which upright tubes of the same bore and numbered 1 to 6 lead off. The

horizontal tube can be closed or opened to any desired extent by means of the stop-cock T. The level of fluid in the reservoir is at all times kept constant by means of the faucet.

If the stop-cock be closed and water poured into the system, the fluid will rise to exactly the same heights in the reservoir and all the side tubes. The heights of the liquid in the reservoir and in the upright tubes represent a certain amount of *potential energy*—energy of position. If the fluid were allowed to flow, a certain proportion of the potential energy would be converted into *kinetic energy*—energy of motion. The total height of the column of fluid in the reservoir is spoken of as the *reservoir head*, H . The height to which the column has risen in a given side tube represents the pressure that is exerted at that point upon the wall of the horizontal tube—that is, the lateral pressure. Thus if the column, say, is 100 mm. high then the lateral pressure in the horizontal tube at that point is obviously 100 mm. of water. In this model the heights of the narrow columns are the same as the reservoir head, therefore the lateral pressure and the total potential energy are of equal value, in other words, the entire potential energy available is exhibited as pressure.

Let us now suppose that the stop-cock is opened to its fullest extent or removed entirely as in figure 34. Let it also be assumed that the outflow of liquid is at a hypothetical maximum—just as though a large opening were made in the bottom of the reservoir chamber—and that there is no friction or other impediment to the outflow. In such an instance the entire potential energy would be transformed into energy of flow (kinetic energy). The fluid would not rise at all in the side tubes; that is, there would be no lateral pressure. The fluid would leave the system at a velocity equal to that which the same body of water would attain if it fell free through a vertical distance equal to its own height, i.e., the height of the reservoir column. From the two foregoing examples it is seen that a given amount of potential energy may remain as such, or, theoretically, be converted entirely into kinetic energy.

In figure 35 the stop-cock is opened. Part of the total potential energy is now utilized in giving velocity to the flow of fluid in the horizontal tube. The remainder is exhibited as lateral pressure which can be expressed as the height in centimeters of the fluid in the side tubes. The velocity of flow (kinetic energy) will increase or diminish and the lateral pressure fall or rise reciprocally. From these considerations it may be stated that: *the greater the velocity of outflow from the system the lower will be the lateral pressure and vice versa.*

When, as in figure 35, the stop-cock is partially open and, as in practice, the flow along the horizontal tube is impeded by friction, the water rises only part way in the side tubes, and not to the same height in each. The level of the column in the first tube is a little lower than that of the fluid in the reservoir which is kept constant by the supply faucet. The second column is

lower than the first, the third than the second and so on, there being a steady decline in the levels of successive tubes. A line joining the menisci is straight, and falls a little below the surface of the fluid in the reservoir.

The difference between the level of the first column and that of the reservoir is evidently due to the flow of liquid along the horizontal tube, since when, as shown in figure 33, there was no flow the two levels were the same. This difference between the height of the reservoir and that of the first column represents the

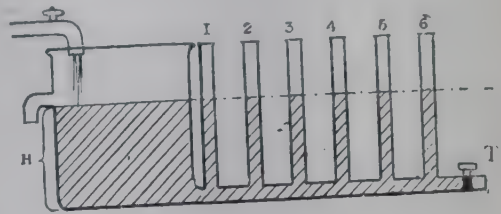


FIG. 33. Description in text.

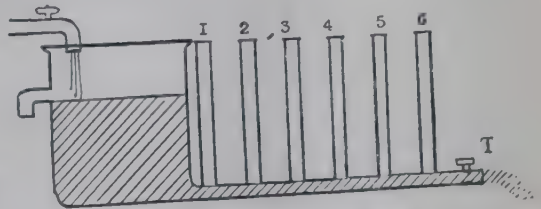


FIG. 34. Description in text.

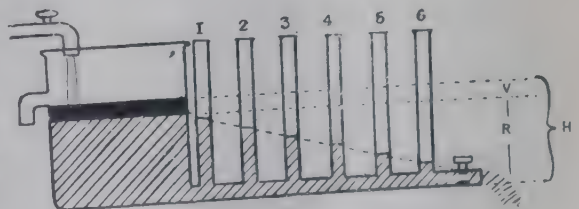


FIG. 35. Description in text.

proportion of potential energy which has been converted to kinetic energy, i.e., which is responsible for the velocity of flow along the horizontal tube. It is therefore termed the *velocity head*, V . That the drop in lateral pressure in tube 1 is actually due to the velocity of the flow may be shown by having its lower end project into the horizontal tube and bent so that its opening faces the stream as in figure 36. When this is done the velocity of the fluid causes the level of column 1 to attain practically the same height as the level of the reservoir column. If the opening is turned in the opposite direction as in tube 3, then the level of the column is depressed an equal distance below its original level as a result of the velocity in the horizontal tube.

The difference in the water levels of successive tubes cannot, however, be explained by a progressively greater amount of potential energy being converted into kinetic energy, the velocity of flow must be the same

throughout the length of the horizontal tube since its bore is uniform and in a given time the same amount of fluid that enters at one end from the reservoir must leave by the other. Furthermore, if a tube (6), say, be extended and turned to face the stream (fig. 36) the fluid in it rises, but the rise in this tube only partially annuls the original fall in its level and is precisely equal to the rise which occurred under the same circumstances in tube 1, i.e., it is equal to the velocity head.

The progressive fall in lateral pressure along the system is due to the energy lost in overcoming friction. At the outlet the lateral pressure has fallen to zero. Evidently then at this point the whole of the potential energy not used in giving velocity to the fluid has been consumed in overcoming frictional resistance. So, R. (fig. 35) will represent this lost energy and is called the *resistance head*. The proportion of energy used in this way is very small in tube 1 since the length of horizontal tube traversed by the fluid is very short, but increases at the expense of the lateral pressure, in proportion to the distance along the horizontal tube

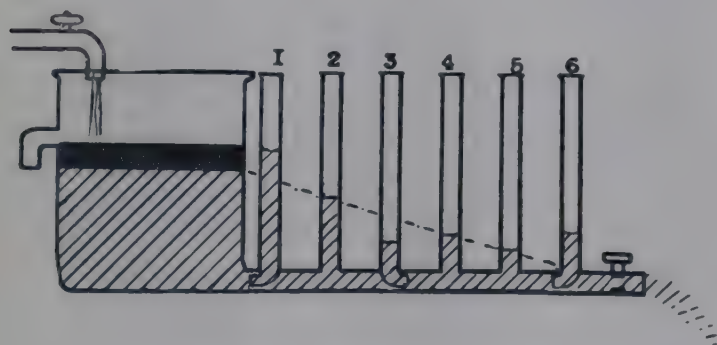


FIG. 36. Description in text

traversed by the fluid and the greater frictional resistance that must therefore be overcome.

If the velocity be increased by further opening the stop-cock and allowing more fluid to flow out two effects will be caused.

(a) The lateral pressures in all the tubes will show a greater fall below the level of the reservoir column since more potential energy will be converted into kinetic energy; the velocity head is increased.

(b) The slope of a line joining the menisci of the fluid columns will be steeper, i.e., the differences in pressure between successive tube levels—the *pressure gradient*—will be greater; more energy will be used in overcoming friction for the resistance due to friction increases approximately in proportion to the square of the velocity. (See 3 below.) Reducing the outflow from the tap will produce the reverse effects.

On the other hand, if the diameter of the outlet from the horizontal tube remain the same but the height of the fluid in the reservoir be raised or lowered, thus increasing or decreasing the pressure gradient, then the velocity will vary proportionately.

Some of the more important laws governing the flow of liquids through rigid tubes of small caliber may now be briefly summarized.

- (1) *Lateral pressure is inversely proportional to the velocity.*
- (2) *Resistance varies with the length of the tube, i.e., is proportional to the frictional surface.*
- (3) *Resistance is proportional, approximately, to the square of the velocity; with a constant velocity the resistance is inversely proportional to the cross area of the tube.*
- (4) *The sectional area of the tube remaining constant, then the velocity of flow of a given fluid is proportional to the pressure gradient.*

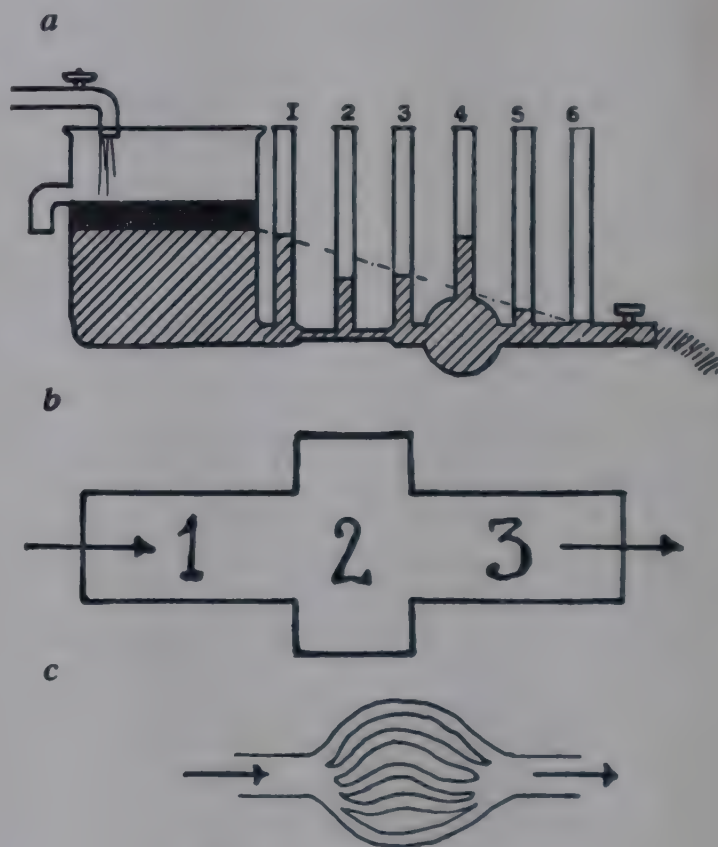


FIG. 37. Description in text.

- (5) *The pressure head remaining constant, then the velocity is directly proportional to the sectional area of the tube, but the quantity of fluid passing through the tube per unit of time—volume flow—is proportional to the fourth power of the diameter of the tube. (Poiseuille law.)*

So far, a model has been dealt with in which the horizontal tube is of uniform caliber throughout. But if the diameter of the tube at any part be increased the velocity of flow through this part will diminish; conversely the velocity will increase through a narrowed section of the tube. We must therefore state a sixth law.

- (6) *In a tube of varying diameter the velocity is inversely proportional to the sectional area.*

In figure 37a, the horizontal tube is shown with a dilated region near its center. Below the model is a more diagrammatic representation (b). The arrows indicate the flow of water through the tube. Obviously since liquids are practically incompressible, the same quantity of water must, in a given time, leave the tube as enters it. Consequently, equal quantities of water

must take the same time to pass any point along the tube. Section 2 of the tube has precisely the same capacity as section 1 or 3. But the length of section 2 is only half that of either of the other sections. It is clear then that the body of water in section 2 has only half the distance to travel as has an equal body in either section 1 or 3. The velocity of the water particles must therefore be reduced by half.

Since the lateral pressure is inversely proportional to the velocity, then the level of the fluid column in tube 4 leading from the dilated section will be higher than the levels of the tubes on either side. These facts explain why an abnormal dilatation in the vascular system, such as an aneurysm or a varicose state of the veins tends to increase. A vicious circle is established and the sacculation tends "to go from bad to worse," since the widened bed of the stream causes a local reduction in velocity and a consequent increase in

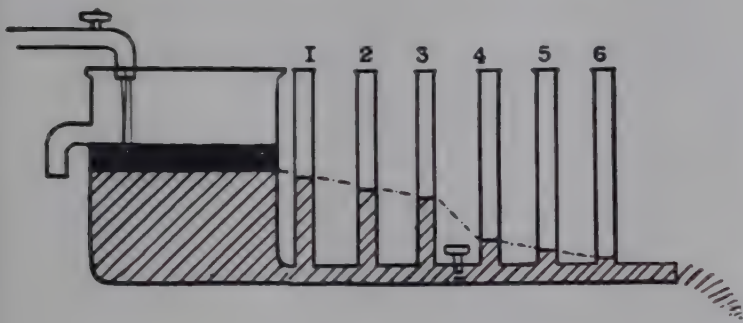


FIG. 38. Description in text.

pressure. This in turn causes a stretching of the vascular walls and further dilatation, and so on.

It is immaterial whether the increase in the cross area of the stream is brought about by a single dilatation or is accompanied by a division of the tube into a number of smaller channels as obtains in the vascular system (cf. fig. 37 c and fig. 41, p. 118). So long as the sum of the sectional areas of all the subdivisions is increased, no matter how small these are individually, a reduction in velocity results.

The horizontal tube of the model in figure 37a is narrowed between the upright tubes 1 and 3. The velocity in this section is therefore increased and the pressure reduced as is shown by the height of the fluid in the second side tube.

In the final model, figure 38, the tap has been placed half way along the horizontal tube so as to divide the system into two sections. If the tap be partially closed, a sharp drop in the curve of lateral pressures will occur between the tubes on the left of the tap, and those on the right. That is, the model has been divided into a high and a low pressure system. Increasing the flow through the tap will, as we know, cause the pressure in the left hand section to fall and the pressure in the right hand section to rise. Reducing the flow through the tap, on the other hand, causes contrary effects in the two systems.

THE APPLICATION OF SOME OF THE FOREGOING PRINCIPLES TO THE CIRCULATION OF THE BLOOD

The heart, of course, is the source of the energy whereby the blood is driven through the system at a given pressure and velocity.

THE ENERGY OF THE VENTRICULAR CONTRACTION— THE WORK OF THE HEART

The energy derived from the contraction of the cardiac muscle is expended mainly in overcoming the frictional resistance which opposes the flow of blood through the systemic vessels from the left to the right side of the heart in the case of the left ventricle, and through the pulmonary circuit in the case of the right. The energy expended in this way and dissipated as heat amounts to from 80 to 95 per cent of the total calculated energy (see below). The remaining fraction of the total energy liberated by the cardiac muscle appears as mechanical or external work. The latter was found by Evans and Matsuoka, employing the heart-lung preparation (p. 214), to amount to 5 or 6 per cent of the total energy when the heart was beating quietly and its output small. This figure, which represents the efficiency of the cardiac machine, is therefore very low under these conditions. The efficiency rises, however, to 20 per cent or higher when, as in muscular exercise, the output of blood from the heart per minute is maximal and the cardiac action is vigorous. That is to say, the efficiency of the cardiac muscle rises up to an optimum load as its work increases. Also for a given load it works more efficiently at slow than at rapid rates.

The total energy expenditure of the cardiac muscle can be calculated from the oxygen consumption of a heart-lung preparation (p. 214). Now, in the consumption of 1 liter of oxygen the heat which is generated amounts to about 5 large calories. The work equivalent of one calorie is 426.5 kilogram-meters (or 3086 foot-pounds). The consumption of 1 liter of oxygen, therefore represents a total energy expenditure of $426.5 \times 5 = 2132.5$ kilogram-meters. The proportion of the total energy expenditure appearing as work gives the efficiency of the cardiac machine. The actual work performed is calculated from the following formula—

$$W = \frac{7}{6} QR + \frac{mV^2}{g}$$

Where W = total work in kilogram-meters per hour, Q = volume of blood expelled in liters per hour, R = mean arterial blood pressure in *meters* of blood. This latter is obtained by multiplying the figure for the

arterial blood pressure in millimeters of mercury by .0135; mercury is about 13.5 times heavier than blood. The pressure in the right ventricle is only one-sixth of that developed in the left so to obtain the value of QR for the whole heart this factor is multiplied by $\frac{1}{6}$.

The factor QR means, in brief, that a certain amount of blood Q is expelled from the heart against a resistance R and that the work done is equivalent to that which would be required to raise the weight of blood through a certain height. This latter corresponds in a given instance as mentioned above to the arterial blood pressure (p. 120). When the output of the heart is small this part of the equation represents by far the greater part of the work performed. When the body is at rest, 99 per cent of the work performed by the heart (which as mentioned above is from 5 to 6 per cent of its total energy expenditure) is employed in raising and maintaining the pressure of blood in the arterial system and in expanding the elastic arterial walls.

The factor $\frac{mV^2}{g}$ represents that portion of the work performed by the heart in giving velocity to the blood. That is, it gives the amount of total energy that is converted into kinetic energy. When the cardiac output is small this factor as just indicated is negligible, amounting to less than 1 per cent of the total work performed.

In the above expression m = weight of blood in kilograms per hour, V = mean velocity of the blood in meters per second at the root of the aorta, g = acceleration due to gravity, a constant amounting to 9.80 meters per second, per second.

It has been pointed out by Evans that since in calculating the kinetic energy of the cardiac contraction it is the mean velocity of the blood as it is expelled from the ventricle, i.e., during the ejection period of the cardiac cycle, that is required rather than the mean velocity of the blood in the aorta throughout the entire cycle, a correction must be employed to obtain the true value. The velocity of the blood issuing from the ventricle rises to a maximum about the middle of, and falls to zero at the end of the ejection period. The velocity varies inversely with the length of this period. Therefore, when the latter has the usual duration of about $\frac{1}{3}$ of the cardiac cycle the value for the velocity of the blood in the aorta must be multiplied by the square of $\frac{3}{2}$ or by 7, approximately. The equation therefore becomes $\frac{7mV^2}{g}$, or the more generally applicable one, $\frac{m \cdot VC^2}{gE^2}$, in which C = duration of cardiac cycle and E = duration of ejection period.

The kinetic factor has the same value for each ventricle, since identical quantities of blood are ejected at equal velocities from each side of the heart at each beat. When the output of the heart is large the kinetic factor can be no longer neglected in calculating the work of the heart. It reaches an importance com-

parable with the pressure factor, QR. The magnitude of these two factors may be compared by the following numerical examples under conditions of small and large systolic outputs respectively.

A. Heart of dog, small output, 6 liters per hour.

Mean arterial blood pressure 100 mm. Hg. Mean velocity of blood at the root of the aorta, 0.085 meters per second.

$$\begin{aligned} W &= \frac{7}{6} QR + \frac{7mV^2}{g} \\ &= \frac{7(6 \times 100 \times 0.013)}{6} + \frac{7 \times 6(0.085)^2}{9.8} \\ &= 9.10 + 0.031 \\ &= 9.131 \text{ kilogram-meters per hour} \end{aligned}$$

B. Forcibly beating heart, with output of 90 liters per hour.

Mean arterial blood pressure 100 mm. Hg. Mean velocity in aorta 1.27 meters per second.

$$\begin{aligned} W &= \frac{7}{6} QR + \frac{7mV^2}{g} \\ &= \frac{7(90 \times 100 \times 0.013)}{6} + \frac{7 \times 90 \times (1.27)^2}{9.8} \\ &= 136.5 + 103.7 \\ &= 240.2 \text{ kilogram-meters per hour} \end{aligned}$$

The kinetic factor in the above example is seen to constitute a large part of the total work performed. If output is still further increased, say to 120 liters per hour, then the value of this factor may exceed the pressure factor QR; it may constitute 60 per cent of the total work. The disproportionate increase of kinetic factor over the QR factor is due to the fact that the latter increases in direct proportion to the output, whereas the former increases as the cube of output. For instance, when as in the above example the output is increased from 6 to 90 liters per hour, that is 15 times, the QR factor is increased to the extent $(9.10 \times 15 = 136.5)$. The value of the kinetic factor, however, is increased over 3000 times since mass of blood is increased 15 times, and V^2 is increased $15 \times 15 = 225$ times, and $\frac{7m(V)^2}{g}$ is increased $15 \times 15 \times 15 = 3375$ times. Thus the value of the kinetic factor in example A is 0.031, in example B an output 15 times greater it is approximately $0.031 \times 15^3 = 103.7$. If the output is increased from a very small magnitude, say of two or three liters per hour, to one very much greater, 120 liters per hour, the value of the kinetic factor in the latter instance will be increased 6000 times or more.

By employing data obtained through indirect measurements of the cardiac output (p. 228) and the blood pressure (p. 125) it is possible to arrive

ation of the work performed by the human heart. The average quantity of blood discharged from the ventricle (Q) when the body is at rest is around 5 liters per second. If the mean blood pressure is 93 mm. Hg then the value of R is 1.35 meters.

Therefore, $\frac{7}{6} \times \frac{60}{1000} \times 1.35 = 0.93$ kilogram-meters per second, or over 5 kilogram-meters per minute, is the work performed by the average heart during rest. With this small cardiac output, the kinetic factor may be neglected. Evans took the diameters of the aortic and pulmonary orifices to be 2.5 cm., the duration of systolic discharge as 0.3 second and the ventricular output as 60 grams per beat, obtaining a figure of 1.35 meters per second as the velocity of discharge during rest.

Then, on the other hand, the output is of large magnitude (over 25 liters per minute) as in strenuous exercise the velocity of the blood as it leaves the ventricle is over 2 meters per second. The kinetic factor calculated from the output and velocity of ejection amounts to over 10 per cent of the total work performed. The latter may reach a value exceeding 10 kilogram-meters—sufficient to lift the weight of an average-sized man some three and a half feet per minute.

In aortic stenosis, with marked narrowing of the aortic ring, the velocity of ejection is greatly increased above the normal even during rest. The work of the ventricle may be nearly doubled, and the increase is due to the enormous increase in the kinetic factor. It may, even in the absence of muscular exertion, almost equal the pressure (QR) factor. That is, the kinetic factor will then increase the work of the heart nearly 100 per cent.

In hypertension (p. 128), R , and consequently the work of the heart, is of course increased.

THE PRESSURES AND VELOCITIES OF THE BLOOD IN DIFFERENT PARTS OF THE VASCULAR SYSTEM

The arteries constitute a high pressure system which is separated from the venous or low pressure system by the *arterioles*. These latter represent the stopcocks in the artificial models (pp. 113–115). The sphincter-like arrangement of the smooth muscle in the walls of these vessels enables their calibers to be increased or diminished; when more blood issues from the arterial system into the capillaries and veins, the pressure in the arteries falls whereas it in the capillaries and veins tends to rise. If the arteriolar calibers diminish, capillary and venous pressure changes of a reverse order result. The pressure throughout the arterial system falls in a gradual slope from the larger to the smaller branches as a result of the greater distance through which the blood has travelled before reaching the latter vessels and, as a consequence, of a pro-

portion of the energy derived from the cardiac contraction having been consumed in overcoming frictional resistance. The pressure fall from the aorta to the small arteries amounts to about 20 mm. of mercury. The greatest fall in pressure occurs beyond these vessels, namely during the passage of the blood through the arterioles. The pressure drop in this part of the circulation amounts to from 50 to 60 mm. Hg. (fig. 39 and fig. 42, p. 121).

Let us now consider the causes of this abrupt fall. We find that when the blood reaches the region of the arterioles the frictional surface is

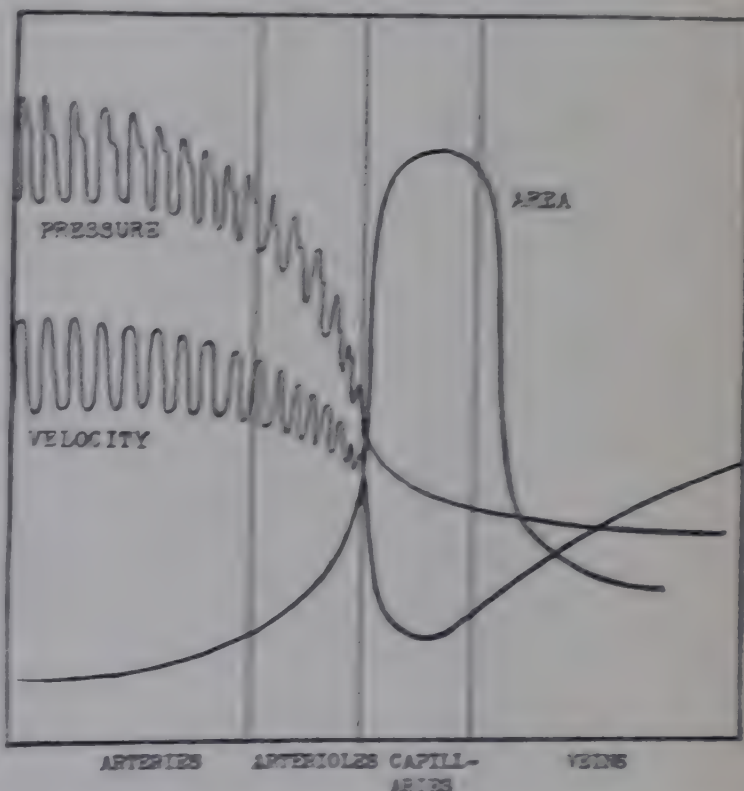


FIG. 39. Diagram showing the pressure and velocity of the blood in different parts of the vascular system (modified from Fredericq). Note the relation between blood velocity and vascular area, and the absence of rhythmical variations in pressure and velocity in the capillaries and veins [see also p. 122].

greatly increased as a result of the breaking up of the vascular bed into smaller channels. Yet the total cross area of the blood stream at this point is not greatly enlarged. As a matter of fact it is increased comparatively little. The distinction may be rendered clearer if reference be made to the diagram (fig. 40). The large circle A represents the circumference of the aorta. The column of blood within has a certain sectional area and a certain surface with which it and the arterial wall are in contact. Frictional resistance is proportional to the extent of this surface. In B, which represents the arteriolar region, a somewhat larger sectional area is composed of the sectional areas of a very large number of separate blood columns.

The sum of all these cylindrical surfaces must be enormously greater than that of the single aortic blood column. Since the total sectional area of

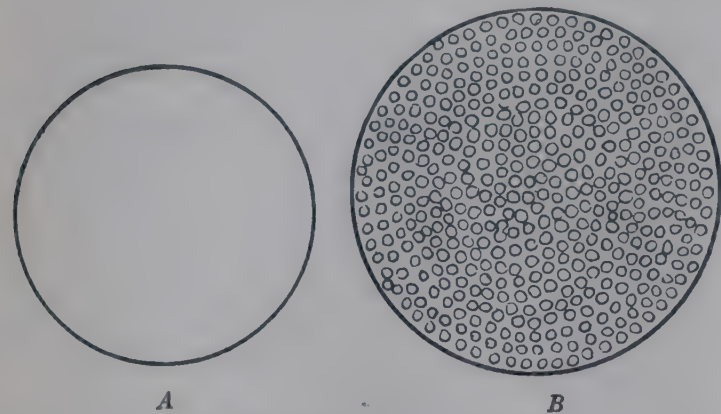


FIG. 40. Description in text.

third layer glides upon the second, the fourth upon the third, and so on. Thus the cross-section of a moving stream consists of a series of concentric layers like the skins of an onion. For this reason simple roughening of the interior of an artery causes little increase in the resistance to the flow of blood. The movement of one layer upon the next diminishes progressively in a central direction so that in the axial portion of the stream the liquid is free from friction and its velocity is maximal. This more rapid movement in the axis of the stream can be observed in blood flowing in the small vessels of a transparent tissue. The corpuscles near the vessel wall progress comparatively slowly while those in the axial stream are swiftly moving. The greater the viscosity which the liquid possesses, the further centrally do the frictional layers extend and the smaller in extent

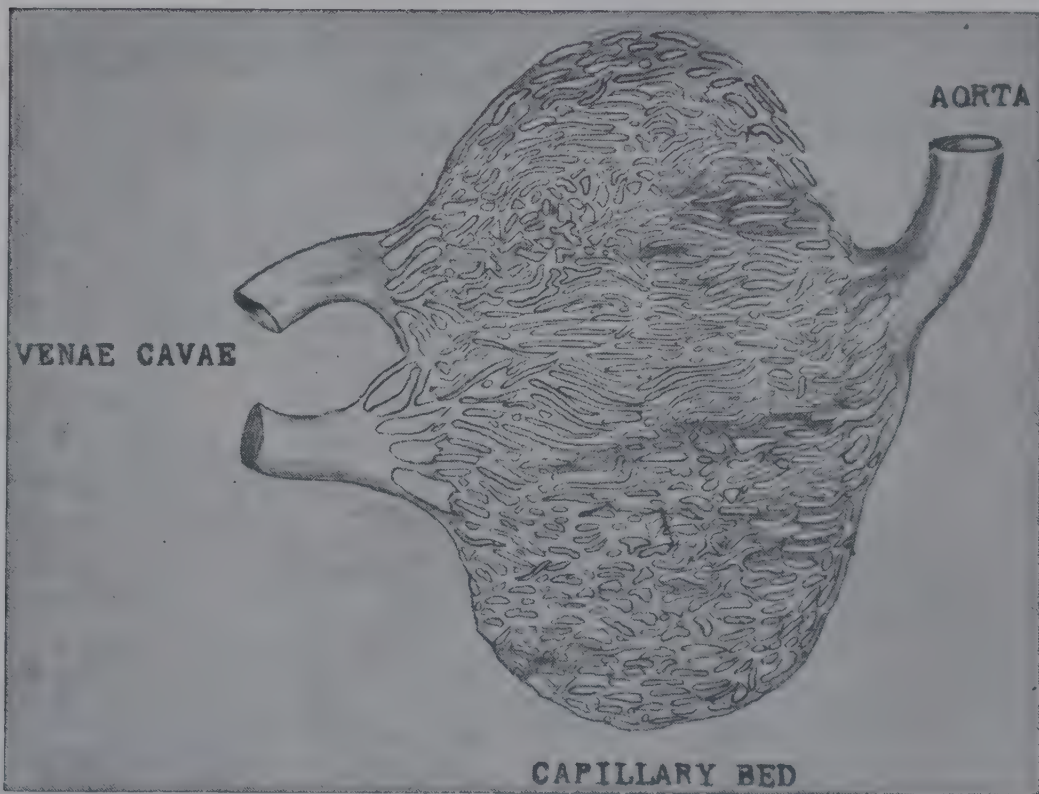


FIG 41. Diagrammatic representation of the expansion of the vascular bed in the capillary area ("capillary lake").

the vascular bed in this situation is only moderately increased, the blood velocity shows only a moderate reduction (p. 114). And, since the frictional resistance is proportional to the square of the velocity, the effect of the increased surface upon the resistance to the flow of blood through the arterioles will be very great.

In the case of liquids flowing in narrow tubes friction is not developed between the moving liquid column and the inner surface of the tube, but between the molecules of the liquid itself. The outer layer of flowing liquid in contact with the lining of a tube is stationary. No friction therefore develops between this layer and the walls of the tube. The tubular layer of liquid next within this stationary layer rides or "slips" upon it, the

is the frictionless "core." For a given liquid the absolute depth of the layers is practically the same whether the diameter of the liquid column is great or small. Consequently in the aorta where the cross area is great the proportion of this wherein friction is developed is quite small as compared with that of the slender blood columns in the arterioles where the greater part of the stream may be occupied by frictional layers.

Beyond the arterioles through the capillaries and veins to the right side of the heart, the slope of pressure is again a gradual one. A further quota of energy is expended in propelling the blood along these vessels against resistance. The latter, though of very moderate degree, is such that by the time the blood has reached the right auricle

the pressure has been reduced to almost zero—about 5 mm. of water (see also p. 137).

The *variations in velocity* throughout the vascular system are quite different from those of pressure (fig. 39). The velocity is high in the arteries (p. 146) but is reduced several hundred times in the capillaries and small veins. In the *capillary area*, though each vessel is extremely narrow, having, on the average, a diameter no greater than that of a red corpuscle, the sum of the sectional areas of these fine divisions of the vascular system is from 600 to 800 times greater than the cross area of the aorta. This broadening of the vascular bed into the "capillary lake" as this area is sometimes called, causes a proportionate slowing of the blood stream (fig. 41). The reduced velocity here has obvious advantages since it is in this region that the interchange of gases and food materials, and of waste products takes place between the plasma and the extravascular fluids. Since the velocity of the blood flow is so greatly reduced the frictional resistance in the capillary region is relatively small despite the narrowness of the individual channels. In consequence any further fall in the pressure of the blood in its passage through the capillary is of moderate degree. It amounts

under ordinary circumstances to only 20 mm. of mercury or less. The slowing of the stream would also have a tendency to raise the pressure in this region (p. 000) and so to counteract, in part at least, for the fall that would result from the increased frictional resistance. After traversing the capillary area the velocity of the blood increases again for, with the confluence of the smaller veins to form vessels of ever increasing size but fewer in number, the total cross area of the vascular bed becomes progressively reduced. The sectional area of the great veins at their point of entrance into the right auricle is only about double that of the aorta. The slowing of the current in the capillaries and its quickening in the veins, though influenced from time to time by other more purely physiological factors to be considered later, are due in the main simply to the differences in the areas of the vascular beds in the two situations. Obviously this must be so since the vascular system is closed and, except as a temporary event when the capacity of a part of the system is suddenly increased or reduced, the same quantity of blood which leaves the left ventricle must, in a given period of time, be emptied into the right auricle.

CHAPTER XV

THE ARTERIAL BLOOD PRESSURE

THE EXPERIMENTAL MEASUREMENT OF THE BLOOD PRESSURE

The pressure in the crural (femoral) artery of the horse is sufficient to raise the blood to a height of between 8 and 9 feet. That is to say, the pressure exerted upon the walls of the artery is equivalent to the pressure exerted by a column of blood of this height. This comparatively great pressure was first demonstrated by the cleric-scientist, the Rev. Stephen Hales of Teddington, England, over two hundred years ago (1733). A long glass tube was connected by means of a goose's trachea (which on account of its flexibility served in lieu of rubber tubing) to a brass cannula inserted into the animal's artery. When the blood was permitted to flow from the artery into the vertical tube it rose rapidly, but with fluctuating progress, until it reached a height of 8'3", and then oscillated above and below this level with each beat of the heart.

In man the normal pressure is considerably less than this, amounting to no more than 5 or 6 feet of blood, but in cases of hypertension (p. 128) the pressure may be sufficient to raise a column of blood to a height of 13 feet. The pressure varies within fairly narrow limits in different warm-blooded species, and there is little or no relationship between the size of an animal and the height of its blood pressure. The pressure in the rat's arteries is actually somewhat higher than that in human vessels and the arterial pressure of a mouse¹ is probably little different from that of an elephant. The blood pressure is, in general, higher in birds than in mammals whereas that of cold-blooded animals is only about one-third. Obviously the method of measuring blood pressure employed by Hales in his pioneer work has great disadvantages, both on account of the technical inconvenience, and the inaccuracy consequent upon the increase in the capacity of the circulatory system which the employment of a long section of tubing involves. For this reason the registered pressure would be considerably less than that actually existing. In order to overcome these faults the blood is not permitted to leave the blood vessel, but is made to exert its pressure upon mercury placed in a U-shaped tube. Since mercury is thirteen and a half times heavier than blood a column of the metal is raised a corresponding fraction of the distance (about 5 inches) that the blood itself would rise. The mercury being confined within a

tube doubled into the form of a U this distance is further reduced by half. The height of the pressure is indicated by the difference in levels of the two limbs of the U. Ever since Poiseuille in 1828 introduced this instrument—the *mercury manometer*—it has been customary to express the pressure of the blood in millimeters of mercury. In order to prevent coagulation of the blood, which was another serious objection to Hales' original method, the tubing connecting the cannula in the artery with the manometer is filled with a solution of sodium citrate, or other anticoagulant fluid. Ludwig improved the method by making it self-recording. He placed a float upon the mercury column, to the float was fastened a long stiff wire bearing a writing point. By having the latter inscribe its movements upon a moving surface—a revolving drum covered with smoked paper (*kymograph*)—permanent tracings of the blood pressure were obtained.

THE SYSTOLIC, DIASTOLIC, MEAN AND PULSE PRESSURES

Hales in describing his experiment speaks of the blood column, after it had ceased to rise further in the tube, oscillating above and below a mean level. To quote his own words, "When it (the blood) was at its full height it would rise and fall at, and after each pulse, 2, 3 or 4 inches." In blood pressure tracings taken by Ludwig's method these same fluctuations in pressure are seen as small waves synchronous with the heart beats (fig. 42). The crests of the waves which represent the maximal pressure correspond to the contraction or systole of the ventricle. The maximal pressure is consequently known as the *systolic pressure*. The troughs of the waves, i.e., the points of minimal pressure coincide with the end of the resting phase or diastole of the cardiac cycle (p. 168). This level is called the *diastolic pressure*. The *mean pressure* is usually given as half the sum of the values for the systolic and diastolic pressures.²

¹ This is not strictly accurate and a true numerical expression in millimeters of mercury of the mean pressure is not simply the average of the values of the systolic and diastolic pressures, i.e., the sum of these values divided by 2 (arithmetic mean). The average pressure throughout the cardiac cycle, i.e., the true geometric mean, is somewhat lower than this, lying nearer the diastolic than the systolic pressure. If the pressure fell in a steady slope from its systolic to its diastolic level throughout the cardiac cycle, and the pulse wave (see fig. 54) inscribed a perfect triangle, the arithmetic and geometric means would be identical. The descending limb of the pulse curve, however,

² The carotid blood pressure (systolic) of the dog is from 120 to 165 mm. Hg, and of the horse from 135 to 150 mm. Hg. The following values for the blood pressures (average systolic in mm. Hg) were obtained by Woodbury and Hamilton for a number of different species; mouse, 113; rat, 187; canary, 220; robin, 118; frog, 43; turtle, 44; and carp, 43. These pressures were determined by means of a hollow needle inserted through the chest wall into the left ventricle.

The difference between the diastolic and systolic pressures is the *pulse pressure*. This, clearly, is caused by the ejection of blood into the aorta during systole. Its magnitude, other things being equal, will vary with the quantity of blood ejected by the heart at each beat.

The diastolic pressure represents the constant load which the arterial walls are called upon to bear and the resistance which the ventricular contraction must overcome to throw open the aortic valves. It shows a steady but slight decline from the larger to the medium sized vessels. The systolic pressure shows a fall between the larger and the smaller arteries which though not great is much more pronounced than that which occurs in the diastolic. On this account the two pressures tend to become more nearly equal toward the periphery, the pulse pressure being reduced. Since the pulse pressure is the difference between

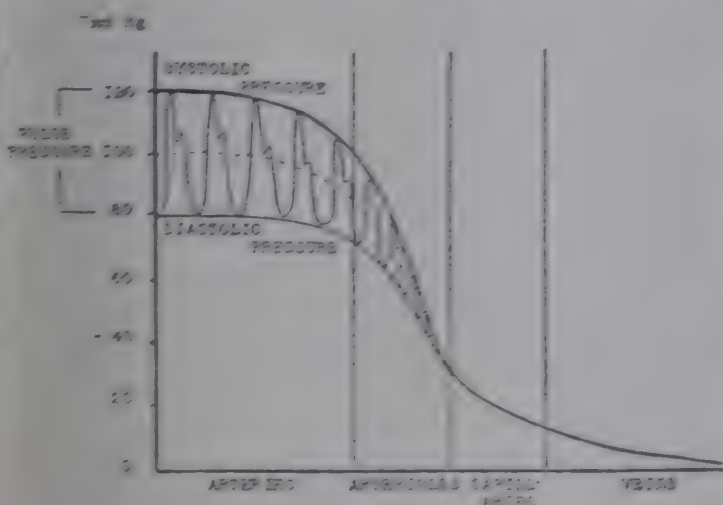


FIG. 42. Showing the phases of the arterial blood pressure.

the systolic and diastolic pressures, it may be reduced by an alteration in one or other of these. A rise in the systolic or a fall in the diastolic will cause the pulse pressure to increase; while a fall in the systolic or a rise in the diastolic, will lower the pulse pressure. If both systolic and diastolic pressures rise or fall to an equal extent the pulse pressure remains unchanged. The mean pressure will rise as a result of a rise in either the diastolic or systolic pressure or of both together and will fall when a reduction of either or of both of these pressures occurs.

THE SEVERAL FACTORS WHICH COMBINE TO MAINTAIN THE NORMAL ARTERIAL PRESSURE

These factors are five in number and though certain points concerning the rôle which some of

presents one or more secondary waves which prevent it from assuming the purely triangular form.

them play in the maintenance of the blood pressure have been touched upon more or less incidentally in previous sections, it will be necessary to consider them here more categorically. They are—

- (1) *The pumping action of the heart*
- (2) *The peripheral resistance*
- (3) *The quantity of blood in the arterial system*
- (4) *The viscosity of the blood*
- (5) *The elasticity of the arterial walls*

(1) *The pumping action of the heart.* The means by which the cardiac contraction exerts its effect upon the arterial blood pressure is, obviously, through the quantity of blood which it is capable of discharging into the aorta in a unit period of time, i.e., upon the output of the heart per minute (minute volume, p. 224). When more blood is forced into the already filled arterial system, it cannot escape at once from the system in the same amount as it is thrown into the aorta, so the arterial walls become stretched. The pressure rises until the velocity of flow through the arterioles is great enough to balance again the outflow from the system with the inflow. Hales grasped this fundamental fact when he wrote, "the real force (pressure) of the blood in the arteries depends on the proportion which the quantity of blood thrown out of the left ventricle in a given time bears to the quantity which can pass through the capillary arteries (arterioles) into the veins at that time."

(2) *The peripheral resistance.* This resides in the arterioles (see also p. 117) and to a less extent in the capillaries. By far the greater part of the peripheral resistance of the circulatory system is constituted by the arterioles of the abdominal viscera—the so-called splanchnic area. Stimulation of the great splanchnic nerve (p. 940) which innervates the rings of muscle fibres in the walls of these vessels causes their constriction, and consequently a reduction in the outflow from the arterial system. As outlined in the last section the pressure will continue to rise until inflow and outflow are again balanced. In the absence of compensatory changes in the other factors concerned in the maintenance of the pressure this remains at the higher level so long as the constriction persists. Dilatation of the vessels, i.e., reduction in peripheral resistance, will of course be followed by the opposite effect. When the vessels of the splanchnic area are fully dilated they are capable of accommodating almost all the blood in the body; in such an event the blood pressure would fall to zero. The peripheral resistance might be compared to a dam in a river. If the dam is raised or lowered the water continues to rise or fall

respectively (and its pressure in consequence increases or diminishes) until it reaches the new level. From then on the quantity of water which overflows in a given time is the same as it was at the original level.

(3) *The quantity of blood in the arterial system.* In any closed system of rigid tubes fluid must fill it to capacity in order that a pressure can be developed within it. The arterial walls are distensible and elastic, and a certain degree of stretching of these must occur before any considerable pressure is created. The arterial system must be actually over-filled and the greater the extent of the over-filling the greater will be the blood pressure. Loss of blood, either of all its elements, as in hemorrhage, or of the fluid portion alone, if not compensated for sufficiently by readjustment of the other factors concerned in blood pressure maintenance, must inevitably result in a fall of pressure. Increasing the total amount of circulating fluid artificially as by the transfusion of blood or blood substitute will elevate the pressure again. Saline solution, however, as explained elsewhere (p. 39) causes a very evanescent rise, since it soon leaks from the vessels into the surrounding tissues. In animals the blood pressure may be lowered by hemorrhage to half its normal value and restored again to its original level by re-introducing into the circulation the blood which has been removed or by the infusion of an effective blood substitute (see Effects of hemorrhage, p. 21).

(4) *The viscosity of the blood.* The greater the viscosity or "thickness" of any liquid the greater is the pressure required to force it along a length of narrow tube in a given time; or if the pressure be constant the longer is the time required for it to traverse the tube. The frictional resistance which is developed between the parts of the liquid itself, that is, the internal friction (p. 118) is greater when the viscosity is high than when it is low. Viscosity depends upon the degree to which the molecules or particles of a fluid cohere. Blood is some 5 times more viscous than water.¹ With regard to the influence of viscosity upon the blood pressure, it is again a matter of outflow through the arterioles. If the driving force remains constant and the caliber of the vessels is unchanged, then the greater the viscosity the greater will be the frictional resistance developed

in this region and the less will be the quantity of fluid that will pass through in a unit of time.

The blood owes its viscosity to its colloids (plasma proteins) and to an even greater extent its suspended corpuscles; friction is developed between the surfaces of the latter and the surrounding fluid. Changes in concentration of the blood as a result of changes in protein content or in the number of its corpuscles therefore alter its viscosity; venesection by removing a quantity of blood and causing dilution of the remainder (p. 16) causes a fall in viscosity which may materially relieve the work of the heart. For these reasons viscosity is low in anemia and high in polycythemia, leukemia and anhydremia. Also changes in its chemical composition or in its gas content may alter its viscosity of the blood. Carbon dioxide increases viscosity oxygen lowers it: venous blood is, in consequence, more viscous than arterial, and high blood viscosity is usual in congestive heart failure with cyanosis. Chloroform anesthesia and narcosis with morphine are said to increase the blood viscosity. It is also raised in hyperglycemia, hypercalcemia and in acidosis.

The viscosity of most liquids is reduced by a rise of temperature—hot syrup flows more freely than cold. In muscular exercise and in fever the blood temperature is raised, the viscosity of the blood is lowered and the work which the heart is called upon to do in overcoming the frictional resistance in the smaller vessels is then appreciably reduced. Blood concentration, however, which occurs to some extent under these circumstances tends to offset the effect of temperature.

(5) *The elasticity of the vessel walls.* This is concerned mainly with the origin and maintenance of the diastolic pressure and with sustaining the mean pressure at a higher level than would be possible in a rigid system under otherwise identical conditions.

The elasticity of arterial tissue does not come into play to any notable extent with a pressure below from 30 to 40 mm. of mercury (fig. 4). Below this level there would be little stretching of the walls of the arteries which would then behave like a system of rigid tubes. At the usual diastolic pressure that exists, however, the walls are stretched and by virtue of their elasticity tend to recoil against the distending force. We have seen that the flow of blood is pulsatile in the arteries. Beyond the arterioles, i.e., in the capillaries and veins the flow is continuous. The conversion of the pulsatile flow to an even one depends upon the existence of a diastolic pressure. The physiological principles involved in the maintenance of the diastolic pressure and the disappearance of the

¹ This is an average figure. Values obtained by different observers for the viscosity of blood, taking distilled water as unity, vary considerably but the majority range between 4.5 and 5.5.

beyond the arterioles may be best illustrated by a simple artificial model similar in principle to that devised by Borelli for the same purpose some 150 years ago.

Figure 44 is represented a bulb syringe, labeled at A, and having a short tube, B, which leads into a basin of water. Leading from the opposite pole of the bulb is a longer tube, C. If the bulb be alternately compressed and released the fluid will be drawn from the basin and discharged at the mouth of the tube. If the walls of the tube be composed of some rigid material, (fig. 44, 1), it will be found that when the pump is worked the fluid issues from the tube in spurts or jets synchronous with each stroke, but no flow occurs between the strokes. An increase in the frequency or force of the strokes does not alter

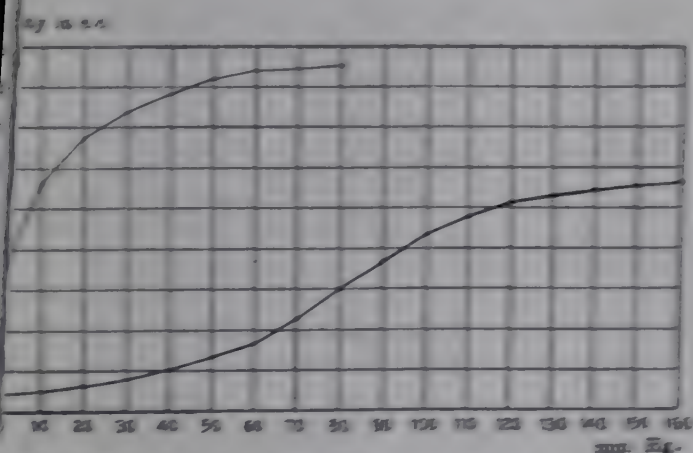


FIG. 43. Curves of distensibility of a vein (upper curve) and of an artery (lower curve). The figures at the left side of the diagram represent the capacity of the vessel when distended under a certain pressure, expressed by the figures on the base line in mm. Hg. (after Starling, constructed from figures given by Guyton).

the intermittent character of the flow nor does lengthening the tubing. If the peripheral resistance of the vascular system be imitated by attaching a nipple of small bore to the mouth of the delivery tube so as to increase the resistance to the outflow of fluid, the issuing stream is finer and its velocity is increased but it still remains intermittent (fig. 44, 2). Let the elasticity of the arterial wall now be imitated by replacing the rigid tube by one of rubber, yet let the mouth of the tube be left free and not constricted in any way (fig. 44, 3). The intermittent character of the stream is unaffected. However, if the small-bored nipple representing the peripheral resistance be fixed into the mouth of the elastic tubing the stream will be found to have lost its pulsatile character and to have become continuous (fig. 44, 4). Two factors are therefore necessary to produce

this result, (a) resistance to the outflow and (b) elastic tubing. The reasons for this are clear. If the fluid has free egress from the tube most of that which enters it from the pump is discharged from the open end before the next beat occurs, the pressure, in consequence, does not rise to a sufficient height to distend the rubber wall, i.e., elasticity is not called into play, over-filling of the tube does not occur, and in consequence the latter acts simply as though it were composed of rigid material.

The foregoing facts apply directly to the arterial system. The elasticity of the vascular walls and the peripheral resistance are both essential for the maintenance of the diastolic pressure. As the contents of the ventricle are thrown into the already over-filled system during systole the added pressure which is then exerted upon the vascular walls causes their further distension. After the completion of systole the elastic walls rebound and

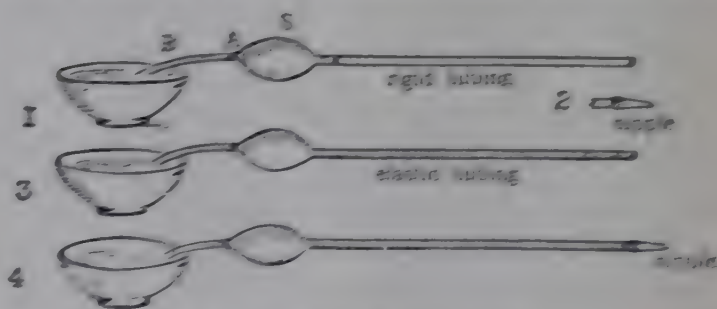


FIG. 44. Description in text.

pressing upon the blood within their embrace force it onwards through the peripheral vessels. In other words, the arterial lumen returns to its previous diameter and the energy that had been stored up during the stretching of the elastic tissue is in this way gradually expended during diastole.

It may then be said that the elastic recoil of the arterial wall acts in a sense as a subsidiary pump to drive the blood onwards in a continuous stream between the heart beats. Otherwise the pressure would fall to zero after each systole.

THE INFLUENCE WHICH VARIATIONS IN SOME OF THE FOREGOING FACTORS EXERT UPON THE DIFFERENT PHASES OF THE ARTERIAL PRESSURE

(1) *Change in heart rate unaccompanied by an alteration in any of the other factors, e.g., output of heart per minute (p. 214), peripheral resistance, etc., will cause a change in the diastolic pressure but relatively little change in the systolic.* During cardiac acceleration, for example, the diastolic period is shortened and less time is therefore allowed for the energy stored in the elastic walls during systole to become converted

into energy of flow during diastole. In other words, the fall in pressure during diastole is halted at a higher level by the earlier arrival of the next beat. A decrease in heart rate will have the opposite effect; with the longer diastole the slope of pressure is enabled to reach a lower level. Since the quantity of blood entering the arteries per minute remains constant the quantity entering at each beat must vary inversely with the change in rate, which accounts for the relatively small change in the systolic pressure.

(2) *Alterations in the quantity of blood discharged per minute by the ventricle.* If little change should occur in the heart rate and other factors remain unaltered, increase in the output per beat of the heart causes a rise chiefly of the systolic pressure. The diastolic pressure is raised less noticeably, consequently the pulse pressure is increased. The explanation for the less pronounced rise in the diastolic pressure is that, as a result of the high pressure at the end of the ejection period, the pressure gradient throughout diastole is steeper and more energy is expended in giving velocity to the blood; of the blood pumped into the arterial system during systole a larger proportion than ordinarily will therefore have passed through the arterioles by the end of diastole.

(3) *Changes in the peripheral resistance* while other factors remain constant. Though these affect both systolic and diastolic pressures they show their influence predominantly upon the latter phase. The diastolic period is considerably longer even in a rapidly beating heart than the ejection period of systole (p. 172) and, as we have seen, the peripheral resistance is an important factor in the maintenance of the diastolic pressure. It follows therefore that any increase or decrease in the outflow from the arterial system will affect this pressure to a greater degree than the systolic. The mean pressure and pulse pressure vary accordingly. Aortic regurgitation produces an effect upon diastolic pressure similar to that caused by a reduction in the peripheral resistance but greater in degree. The mechanical principles involved are similar; an increased quantity of blood passes from the arterial system during diastole as a result of leakage through the incompetent aortic valves. The peripheral vessels are also usually dilated, which, combined with the high pulse pressure, may cause the appearance of a pulse in the capillaries especially if their emptying be aided by holding the arm above the heart level. Slight pressure upon a superficial capillary area such as at the base of the finger nail may then show alternate blanching and flushing synchronous with the heart beat (see also p. 271). In aortic regurgitation the pulse pressure attains a magnitude seen in no other condition (80 or 110 mm. Hg) for not only is the diastolic pressure much reduced but the systolic pressure is raised as well, owing to the greater volume of blood ejected at each heart beat—that which has regurgitated through the aortic valves plus that

received from the auricle. Also for these reasons, the carotids throb visibly and the pulse is of the collapsing type (water hammer or Corrigan's pulse) that is, when the subject's wrist is held above the shoulder a short forcible impulse is felt during systole but the pressure is not sustained, and falling precipitately during diastole, leaves the artery empty beneath the finger. A pulse tracing shows a wave of large amplitude with a high sharp systolic peak and a steep diastolic decline. An arterio-venous aneurysm produces similar effects (p. 226) upon the arterial system.

(4) *Changes in blood viscosity*, other factors remaining unchanged, tend to affect the diastolic pressure in a manner similar to changes in the calibers of the peripheral vessels.

(5) *Increase in blood volume* will raise both pressures, as a result of the overfilling of the arterial system and greater stretching of the elastic walls.

(6) *Reduction in elasticity of the arterial walls.* Obviously a condition, such as arteriosclerosis which renders arteries less resilient and more like rigid tubes will tend toward a lowering of diastolic pressure (p. 122). Yet as a matter of fact, in arteriosclerosis the diastolic pressure may be raised rather than lowered, since there is frequently an associated narrowing of the peripheral vessels which more than offsets the hardening of the walls of the larger arteries. When, however, the sclerosis is confined to the larger vessels and their branches while the peripheral vessels are free from proliferative changes which narrow their lumina the diastolic pressure is lowered. Diminished distensibility of the vascular walls tends to increase the systolic pressure.

In the foregoing paragraphs variations in the several blood pressure factors and their effects have each been considered as being the only variable in a particular instance. The object of this was to disclose the value of each and the manner in which it acted. Yet it must be remembered that such a description is more or less artificial and that in health and even to a large extent under pathological conditions the various factors interact with one another—there is a give and take among them. When a change in the value of one factor occurs, readjustments of others take place to regulate the blood pressure and keep it within the normal limits. For instance, dilatation of the vessels in one area may be accompanied by vasoconstriction in another (p. 246). Reduction in blood volume as by hemorrhage, is followed by constriction of the peripheral vessels (p. 22), while increased blood volume or a rise in viscosity will likely be followed by the opposite effect upon the vessels.

CHAPTER XVI

THE BLOOD PRESSURE IN THE HUMAN SUBJECT

METHODS OF MEASUREMENT. THE VENOUS BLOOD FLOW

It is evident that any method for the measurement of the human blood pressure must be indirect. The principle employed consists in balancing air pressure against the pressure of the blood in the brachial artery and then estimating the former by means of a mercury or an aneroid manometer.

The instrument used for this purpose includes a flat rubber bag covered by an undistensible envelope of cotton fabric. The cavity of the bag is connected by a length of rubber tubing with the manometer and by another tube with a hand bulb or small pump. By this means the bag can be inflated to any desired pressure. A small valve between the bulb or pump and the bag permits the escape of air, and the reduction of the pressure as required. The uninflated rubber bag (usually referred to as the cuff or armlet) which should be at least 12 cm. wide is wrapped snugly around the upper arm just above the elbow. The bag is then inflated until the air pressure within it overcomes the arterial pressure and obliterates the arterial lumen. The pressure is increased a little beyond this point and is then cautiously reduced again,¹ by the release of the valve, until the arterial pressure just overcomes the air pressure and blood escapes beyond the cuff into the peripheral section of the artery. At this instant the pressure in the bag is read from the manometer. Since the air pressure practically balances the systolic arterial pressure the manometer reading must indicate the value of the latter. It is essential to the method that the manometer reading be taken at the instant when the blood escapes beneath the cuff.

One of two methods, the *palpatory* or the *auscultatory*, may be employed to determine the latter.

(1) *The palpatory method.* In this method the examiner takes the moment that the pulse is felt at the wrist as the index of the systolic pressure. This method is now rarely used since it lacks accuracy. It assumes that the first escape of blood beneath the cuff will cause pulsation in the peripheral artery, but there is no evidence that the amount of blood which escapes beneath

Should deflation be carried out too rapidly the mercurial type of clinical manometer shows a considerable lag, due to the time required for the air above the mercury column to reach atmospheric pressure. The rate of deflation should not exceed from 2 to 3 mm. Hg per second.

the cuff when the artery first opens is sufficient to produce a pulse wave detectable by the finger. Definite pulsation may not occur until the cuff pressure has been lowered 5 to 10 mm. below the point when the artery first becomes pervious. This method therefore gives readings that are too low. Another disadvantage of the palpatory method is that the diastolic pressure cannot be measured satisfactorily.

THE AUSCULTATORY METHOD

In this method, which was introduced in 1905 by the Russian physician Korotkow, certain sounds heard during auscultation of the brachial artery below the cuff are employed as the criteria for the systolic and diastolic pressures. Under ordinary circumstances if a stethoscope be placed upon the brachial or any other artery, no sound can be heard, the flow of blood along the arterial channels being inaudible. If however the artery be compressed by the manometer cuff so as to completely arrest the flow of blood for a moment, a sharp light tapping sound in rhythm with the heart beat will be heard when the pressure in the cuff is again released and falls just sufficiently to permit the arterial lumen to open and allow a jet of blood to pass beyond. As the pressure in the cuff is progressively lowered the sound undergoes a series of changes in quality and intensity.

Four phases of the sound, each having its distinctive character may be heard in succession, in the normal individual, as the pressure is gradually reduced from about 120 to 80 mm. of mercury or less. These are given below with the average pressures at which they are normally heard:

Sounds of Korotkow

- | | |
|------------|---|
| Phase I. | Sudden appearance of a clear, but often faint, tapping sound growing louder during the succeeding 10 mm. Hg fall in pressure. |
| Phase II. | The sound takes on a murmurish quality during the next 15 mm. fall in pressure. |
| Phase III. | Sound changes little in quality but becomes clearer and louder during the next 15 mm. fall in pressure. |
| Phase IV. | Muffled quality lasting throughout the next 5 to 6 mm. Hg fall. After this all sound disappears. |

The beginning of the first sound is taken as the *index of systolic pressure*. As it is quite faint at its commencement it may not be caught at its first appearance by the ear of the inexperienced, or if the observer's hearing is distracted by other sounds. The sound then will not be picked up until the pressure has dropped below the level at which it could be heard in quiet surroundings and the blood pressure reading will be too low.

The fourth sound just before its complete disappearance is taken as the *index of the diastolic pressure*. This sound coincides with the moment that the blood escapes beneath the armlet in a continuous stream rather than intermittently.

The measurement of blood pressure in man is attended by certain inaccuracies dependent upon the resistance of the tissues of the part and, under certain conditions, of the arterial wall itself to the compressing force. These fallacies are to a large extent mitigated by the use of a broad armlet (12 cm. in width), as first introduced by von Recklinghausen, which distributes the applied pressure over a wide area. In a person with normal arterial walls the pressure as measured is probably very close to the true systolic pressure. Variations in the resistance of the arterial wall in different individuals as a result of sclerotic changes or simple hypertonus of the muscular coat may lead to error and give readings that are too high. Repeated compression and decompression just before the actual determination is made will, as a rule, soften the artery or remove the spasm of its walls sufficiently to eliminate this source of inaccuracy. Even when definite arteriosclerosis exists approximately correct estimations of the blood pressure are obtained when this precaution is taken. Though lower readings as a rule are not obtained in a normal individual by repeated readings, in others with apparently normal arteries the reading obtained after the third or fourth trial may as a result of the reduction in tone of the vessel wall be lower by several millimeters than the initial observation.

RELATIVE VALUES OF SYSTOLIC AND DIASTOLIC MEASUREMENTS

The systolic pressure is subject to wider variations under ordinary conditions of health than the diastolic, it also varies more with local arterial changes; for these reasons less reliance can be placed upon it than upon the diastolic. A knowledge of the diastolic level is also of greater value for other reasons. (1) It represents the constant load which the vascular walls are carrying, not only in the larger arteries but throughout the arterial system, for it will be recalled that the fall in systolic pressure from the large to the small arteries is considerable, whereas the diastolic shows

comparatively little change. (2) It also reflects more accurately the state of the peripheral vessels for as already pointed out (p. 124) the systolic pressure responds less to variations in the peripheral resistance.

THE RELATION OF THE PULSE PRESSURE TO THE CARDIAC OUTPUT

The pulse pressure, other factors remaining the same, varies with the amount of blood ejected into the aorta per beat, and we know that the work of the heart depends chiefly upon the amount of blood ejected per minute against the mean pressure in the aorta. It follows therefore that provided the peripheral resistance, blood viscosity and other factors concerned in the maintenance of blood pressure remained constant the product of pulse pressure and heart rate ($PP \times HR$) might be used as an index of the energy of the ventricular contraction. Erlanger and Hooker found that the product tended to remain constant under ordinary physiological conditions, which would not be expected to alter the cardiac output, an increase or decrease in heart rate occurring to compensate for changes in pulse pressure. The index in an individual having the usual pulse pressure of 40 and a pulse rate of 72, would be $(40 \times 72 =) 2880$. Conditions causing a pronounced rise or fall in the cardiac output, on the other hand, are accompanied by a corresponding change in the product. The index has therefore been used as a rough clinical gauge of the minute volume of the heart, and so as a guide to the manner in which the heart is performing its work in diseased states. The index may be of value in following the course of an individual case if the observations are made at comparatively short intervals and the conditions to which the patient is exposed remain practically the same from one observation to the next. No absolute or quantitative value can, however, be attached to it, nor can the results obtained in different individuals be compared with one another.

Miss Skellern has endeavored by means of animal experiments, using the heart lung preparation, to determine the practical value of this index. She could find no constant relationship between the cardiac output and the product of pulse pressure and pulse rate, concluded therefore that no reliance could be placed upon it. The ratio of the index to the output varied from 6.5 to 47. Her results show, however, that in a given experiment in which the peripheral resistance was kept constant the disagreement was not nearly so great as this, and that the index and the output were altered in the same direction. That is, an increase in output was followed by a rise in the value of the index and vice versa. That, as a matter of fact, is practically all that has been claimed for the test. It is considered only as a means of arriving at a general idea of improvement or otherwise occurring in cardiac behavior during the course of an illness. Bearing in mind its limitations, and the restrictions based upon its use

its value may be conceded. *Asperly and Cary* data for regarding the P/P (brachial) $\times P/R$ as a index of the blood flow through the arm.

THE NORMAL ARTERIAL BLOOD PRESSURE

The average systolic pressure of young male is usually given as 120 mm. Hg; the diastolic 80, the mean pressure as 93 and the pulse pressure as 40. The pulse pressure is therefore half of the diastolic and one-third of the systolic, and the normal ratio of systolic, diastolic, pulse pressures is 3-2-1. This ratio holds only at these levels, being altered if the pressures are much above or below the foregoing figures. *Robinson and Brucer* conclude from a study of nearly 1100 persons that the range of normal blood pressures is from 90 to 120 mm. Hg systolic and 60 to 80 mm. Hg diastolic. They contend that blood pressures above the upper levels just mentioned cannot be considered as normal at any age. Slight diurnal variations in blood pressure of from 5 to 10 mm. Hg systolic occur, the peak being in the afternoon and the lowest level in the early hours of the morning.

VARIATIONS IN THE BLOOD PRESSURE UNDER PHYSIOLOGICAL CONDITIONS

Age, sex, and build

Age exerts a definite influence upon the blood pressure levels. At birth the systolic pressure measures from 20 to 60 mm. with an average of 40 mm. It rises rapidly, however, and has an average value of about 70 mm. at the end of a fortnight and 80 mm. at the end of a month. A slow steady rise takes place from this time until about the twelfth year when it averages 105 mm. With the onset of puberty a more sudden rise occurs, which in boys, reaches 120 mm. at about the age of 17. In girls, there is an increase in systolic pressure to the fifteenth year, then a decline to the eighteenth; it remains fairly steady from then on or shows a gradual rise. It has usually been considered that a steady though not great rise in blood pressure from adolescence to old age is the rule in health; the averages for the age of 60 being given as about 140 systolic pressure and 87 diastolic. In men, it is usually stated that a rise of about 0.5 mm. in the systolic and 0.2 mm. in the diastolic and pulse pressure occurs for each year of age after 20 (see table 15) but, from the observations of *Robinson and Brucer*, mentioned above, it is debatable whether this increase with age can be considered to be a physi-

ological or normal phenomenon. In women up to the time of the menopause the systolic pressure is from 4 to 5 mm. lower than for men of the same age. At the menopause, however, there is a somewhat abrupt rise and the pressure remains a little above the male average from then onwards.

Symonds and others have found a correlation between the systolic pressure and obesity. Comparing groups of overweight and normal individuals the former were found to have a pressure on the average 7.5 mm. higher than the latter. In markedly obese but otherwise healthy persons the difference was even more pronounced. The incidence of abnormally high blood pressure (hypertension) is also definitely greater in persons of overweight.

Robinson and Brucer claim that body build is correlated with the blood pressure level. They found in an examination of a large number of persons that in any weight group broad-chested persons on the average had a higher blood pressure (both systolic and diastolic) than had those of slender build.

The effects of digestion, emotion, exercise and posture

Digestion. The systolic pressure is influenced to a small but definite extent by meals. A rise of from 6 to 8 mm. is the usual effect, and this lasts for an hour or so. There is little change in the diastolic pressure. If anything it is reduced, presumably a result of vasodilation in the digestive organs and splanchnic.

Emotional Influences, excitement, fear, worry, etc. markedly affect the arterial blood pressure, especially the systolic. The effects are brought about through increased cardiac action and changes in the state of the vessels through impulses playing upon the cardiac and vasomotor centers in the medulla. The liberation of adrenaline into the blood stream may also be a factor. Quiet restful sleep, according to *MacWilliam*, is accompanied by a fall of from 15 to 30 mm. in the systolic pressure. The fall is most marked during the first hours, rising gradually again after this until the time of waking. *MacWilliam* observed that if the sleep was disturbed and accompanied by imaginary motor activities there might be no depression of the pressure, but rather an elevation, in some instances to as high as 200 mm. systolic and 105 mm. diastolic.

EXERCISE. Of all physiological conditions this, if of a strenuous nature, has the most powerful effect upon the arterial blood pressure. During the muscular effort or even immediately before,

i.e., at the instant that the exertion is contemplated, the pressure commences to rise and reaches a height of 180 or 200 mm. The diastolic pressure shows a less pronounced rise (100 to 110) so that the pulse pressure is increased. In light exercise the diastolic pressure may remain at the normal level while the systolic rises several millimeters. Immediately after the exercise the pressure drops momentarily to normal or even slightly below. It then mounts rapidly to its previous high level, from which it gradually declines again, and in a healthy person reaches the normal within from 1 to 4½ minutes. The evanescent drop in pressure is explained by Cotton, Lewis and Rapport as being due to the sudden relaxation of the abdominal muscles. The blood is drained into the

TABLE 15
The average variations of blood pressure (after Hunter's compilation of observations on a quarter million healthy Americans)
(After Gager)

AGE	SYSTOLIC PRESSURE	DIASTOLIC PRESSURE	PULSE PRESSURE
10	103	70	33
15	113	75	38
20	120	80	40
25	122	81	41
30	123	82	41
35	124	83	41
40	126	84	42
45	128	85	43
50	130	86	44
55	132	87	45
60	135	89	46

venous reservoirs. These when deprived of their support (abdominal muscles) have their capacity increased and the blood flow into the right heart is temporarily reduced. It is not until an appreciable time has elapsed to enable the increased venous capacity to become filled again by blood pouring in from the recently active muscles that an adequate flow into the right heart is restored (p. 130). These responses are much more pronounced and the final decline of pressure to normal levels is postponed if the exercise is carried out in a rarefied atmosphere, or if a condition of "irritable heart" exists.

POSTURE. The diastolic pressure is somewhat higher in the standing than in the sitting position and lowest in recumbency. This change is found to occur whether the postural change is brought about actively or passively and is evidently an

over-compensation for the gravity effect (p. 138). The systolic pressure usually rises but to a less extent than the diastolic, so the pulse pressure is reduced. Reverting from the standing to the sitting or recumbent position has the reverse effect: fall in diastolic pressure and rise in pulse pressure. In persons with an abnormally and habitually low blood pressure, the systolic pressure may actually rise in the lying-down position and fall when the subject stands. The diastolic, on the other hand, is always lowered in recumbency and raised in the erect posture.

PATHOLOGICAL VARIATIONS IN THE ARTERIAL BLOOD PRESSURE

The blood pressure may be persistently above or below the normal range. These departures from the normal are termed *hypertension* or *hypotension*, respectively. It is difficult to make a sharp separation of the normal from the abnormal but an elevation above the average normal for particular age, of 15 mm. in the systolic and 8 mm. in the diastolic may be considered to be definitely abnormal. A reduction below 110 mm. in an adult male (or 100 mm. in adult female) of any age is usually termed hypotension.

ARTERIAL HYPERTENSION

A high blood pressure accompanies such conditions as increased intracranial pressure, *hypothyroidism* and *adrenal tumor or hyperplasia* (p. 691). In these, the hypertension is more or less incidental or of subordinate importance to the primary disease. In the first of these conditions the heightened pressure is apparently due to generalized vasoconstriction resulting from reduced oxygen supply to the vaso-motor center (p. 292). Cushing pointed out that the increased pressure within the cranial cavity caused compression of and slowing of the blood flow through the vessels supplying the medulla. In animals also, a pronounced rise in blood pressure may be induced by *asphyxia* (p. 248), the increased hydrogen ion concentration of the blood acting as stimulus to the vaso-motor center. Permanent hypertension has been produced by the injection of an inert substance such as kaolin into the *arteria magna of rabbits* (Dixon and Heller) thus interfering with the blood supply to medullary centers, and cerebral anemia produced by ligation of the carotids and vertebrals in *hypertension in the dog*. In *hyperthyroidism* hypertension is associated with an increased cardiac output. Temporary rises in blood pressure

in attacks of *angina pectoris*, in *lead colic* and the *crises of tabes*. The hypertension associated with adrenal tumor or hyperplasia is usually paroxysmal character and is due to liberation of excessive amounts of adrenaline (p. 691).

The types of hypertension under consideration in this section are (1) that *secondary to renal disease*, and (2) *essential or primary hypertension*.

1) *Hypertension secondary to renal disease*.—Earlier or later in chronic glomerulo-nephritis the general blood pressure rises, the left ventricle hypertrophies and the arterial tree shows degenerative changes (atherosclerosis).

ETIOGENESIS. It is a well attested fact that in some forms of the disease as well as in primary essential hypertension increased peripheral resistance is the immediate causative factor. The increased resistance is mainly in the splanchnic (Abramson). None of the other factors which have been enumerated in the last chapter maintaining the normal blood pressure exerts an excessive influence in these hypertensive states. The hypertrophy of the heart, for example, is merely secondary—a physiological compensation rendered necessary, as first suggested by Richard Bright (1827), by the greater resistance offered to the flow of blood through the peripheral vessels. Divergent views have been held as to the manner in which the increased peripheral resistance is brought about. Of the theories which have been proposed two require some mention. A brief account will serve as a background to a description of modern researches upon the subject.

(a) *Reduction in size of the vascular bed of the kidney* as a result of structural narrowing of the renal arterioles and the destruction of large numbers of glomerular capillaries. Such changes, it was presumed, would narrow the outlet from the arterial to the venous system. There is no evidence that a localized increase in peripheral resistance of this nature is responsible for hypertension, for in most animals (but excepted) removal of a kidney and part of the other has little or no effect on the blood pressure. Anderson reduced the renal mass in rabbits to the point where severe renal insufficiency resulted without causing any rise in blood pressure. From the great adaptability of the circulation this is what one should be led to expect, the removal of a vascular area from one part of the body being readily compensated for by the opening of collateral channels elsewhere.

(b) *The extension within the circulation of a specific substance produced by the kidney.* Tigerstedt and Bergquist (1918) obtained a pressor substance from normal kidney tissue of rabbits. They postulated that deterioration of this material in kidney disease and its

accumulation in the circulation was responsible for a generalized vasoconstriction. The fact that renal insufficiency caused by the removal of kidney tissue is not productive of hypertension is in harmony with such a theory, for the production of a pressor substance would also be reduced by the operation. On the other hand, Goetz and Dragstedt found that animals in which the urine had been diverted into the terminal ileum or directly into the blood showed no elevation of blood pressure, though they were observed for periods ranging from 11 days to 5 weeks. Yet, as will be seen presently, the conclusions of Tigerstedt and Bergquist came remarkably close to the modern conception of the production of hypertension in renal disease.

THE PRODUCTION OF HYPERTENSION BY REDUCING THE BLOOD FLOW THROUGH THE KIDNEY

Though others had reported that compression of the renal arteries in animals caused a rise in blood pressure, Goldblatt and his associates were the first to show that this procedure causes consistently pronounced and permanent hypertension. Constriction of the renal artery is effected by means of a specially devised adjustable silver clamp. Ischemia of one kidney, produced in this way, the other remaining intact, causes a moderate elevation of the blood pressure which commences three or four days after the operation, but persists for only a short time, returning to the normal level after a month or so. If, on the other hand, both renal arteries are constricted or if one alone is clamped and the opposite kidney removed, permanent hypertension results. The severity of the hypertension varies with the degree to which the renal blood flow has been curtailed. Unless the compression of the renal artery is extreme and, in consequence, the ischemia of the kidney very severe, the elevation of the blood pressure is not accompanied by any detectable impairment of renal function and the kidney shows little histological change. But with severe constriction of the artery, renal insufficiency develops and the animal may die in uremia.¹ The

¹ Hypertension has also been produced by partial obstruction of the ureters, or by renal tumors caused by exposure of the kidneys to X-rays or by the injection of a nephrotoxic agent such as uric acid. On the other hand, the production of multiple aneurysms in the renal vessels, as by injections of liquid paraffin or carbon particles, is not followed by elevation of the blood pressure. Hypertension also follows constriction of the aorta above the origins of the renal arteries. Page found that hypertension develops within four to six weeks after a kidney has been wrapped loosely in cellophane or silk. These coverings set up a chronic inflammatory reaction (peritonitis) which results in the formation of a firm fibrocartilaginous capsule enclosing the kidney. The hypertension is the result, appar-

hypertension and renal failure are accompanied by widespread degenerative changes in the systemic arterioles, the arteriolar walls in many instances showing hyaline degeneration and necrosis. Such a state of the vascular system, taken together with renal insufficiency and the elevated blood pressure, is closely comparable to malignant hypertension as seen clinically (p. 136). Goldblatt was unable to produce arteriolar degeneration in the kidney itself for the simple reasons that, (a) a severe degree of hypertension could not be produced as long as one non-ischemic kidney remained in place, and (b) the vessels of the ischemic kidney are protected from the destructive effect of the hypertension by the compressing clamp, i.e., they lie within a region of low pressure. Wilson and Byrom have succeeded, however, in producing severe hypertension (up to 260 mm. Hg) in rats by constricting one renal artery and leaving the opposite kidney *in situ*. Severe vascular damage, consisting of hyaline or fibrinoid degeneration and necrosis of the walls of the arterioles of the intact kidney (especially of the afferent glomerular vessels) as well as of the systemic vessels, was observed. There was no definite evidence that renal insufficiency played a part in the production of the vascular lesions, though renal failure occurred ultimately as a consequence of the arteriolar damage.

THE MECHANISM INVOLVED IN THE PRODUCTION OF HYPERTENSION BY RENAL ISCHEMIA. It has been definitely established that the hypertension produced by hindering the blood supply to the kidney is due to a vasoconstrictor (pressor) substance produced in the ischemic organ. The hypertensive effect is not dependent upon nervous mechanisms (e.g., a reflex through afferent endings in the kidney, the vasomotor center and vasoconstrictor fibers to the systemic vessels) for it occurs after denervation of the kidney, or section of the splanchnic nerves or of the anterior spinal nerve roots. Even complete excision of the sympathetic chains or destruction of the spinal cord does not prevent the development of hypertension nor materially alter its course after it has been established. Furthermore, hypertension results if

ently, of the renal ischemia induced by the compression of the vessels within the kidney by the newly formed tissue. Contemporaneously and independently, Greenwood, Nassim and Taylor observed that if one kidney was surrounded by a closely fitting cast of gauze stiffened by impregnation with collodion, hypertension occurred *within a few hours after the removal of the opposite kidney* and persisted indefinitely. No rise occurs as long as the other kidney remains undisturbed.

one kidney which has been transplanted into the inguinal region or into the neck (renal artery to carotid, renal vein to jugular) is made ischemic and the other kidney then excised. The transplanted kidney is, of course, completely isolated from nervous control. The inability of such denervation operations to prevent or modify the hypertensive effect proves conclusively that it is mediated through a pressor substance circulating in the blood stream and, further, that the latter acts, not through the vasomotor center, but either directly upon the peripheral vessels or through the intermediary of one or other of the endocrine organs (see below). The substance formed in the ischemic kidney which is responsible for the hypertensive effect is called *renin*, the name already mentioned as having been originally used by Tigerstedt and Bergman. Renin itself, as we shall see presently, is free from any pressor action. It is an enzyme. It is non-dialyzable and thermolabile being destroyed above 56°C. Its substrate (see angiotonin precursor, below) is also thermolabile and is probably a pseudoglobulin.

Difficulty has been experienced in demonstrating in a direct way the presence of a pressor substance in the circulation of the hypertensive animal. The blood pressure of a normal dog is not elevated by transfusing it with the blood of one with renal hypertension. Extracts of ischemic kidneys have yielded uncertain results, for renin is present in the normal kidney though in somewhat smaller amounts it is claimed, than in the ischemic organ. Transfusion and crossed circulation experiments have yielded conflicting results. Katz and his colleagues transfused non-hypertensive nephrectomized dogs with the blood of hypertensive animals over a period of 18 hours but observed no rise in the blood pressure of the recipient animals. On the other hand, Solandt, Nassim and Cowan have reported that when by means of a specially designed pump large volumes of blood were transfused from a hypertensive to a non-hypertensive nephrectomized animal, a temporary rise in blood pressure resulted.

Nevertheless, important evidence of the production of a vasoconstrictor substance in the ischemic kidney has been furnished by the experiments of Houssay, Fasciolo and Taquini. They found that the blood pressure of a non-hypertensive, nephrectomized animal was raised when the ischemic kidney of a hypertensive animal was transplanted into its neck, whereas the transplantation of the kidney of a normal animal gave a

negative result. They also showed that the plasma of blood collected from the vein of an ischemic kidney, as compared with that from a normal one, was markedly vasoconstrictor when perfused through the vessels of the toad.

Renin has also been found in the circulation of hypertensive patients and in the blood of animals with renal hypertension. A rise in the concentration of renin in the blood has been observed in animals suffering from surgical shock, following hemorrhage and in other states associated with a profound fall in blood pressure. Such observations suggest very strongly that the liberation of renin by the normal kidney is a factor in the regulation of the blood pressure, aiding in its restoration to higher levels when it becomes greatly lowered.

THE ACTIVE VASOCONSTRICTOR AGENT. Helmer and Page found that the more purified preparations of renin were inactive. When perfused with Ringer's solution through the vessels of an isolated organ such as the rabbit's ear or dog's tail, such preparations showed little or no vasoconstrictor action. The addition of plasma, blood or serum globulin to the purified renin preparation restored its vasoconstrictor property. Blood or plasma, therefore, contains a material which Helmer and Page originally called renin activator but is now referred to as *angiotonin precursor* and is believed to be a pseudoglobulin. The active vasoconstrictor substance itself i.e., the product of the action of renin upon the serum globulin is called *angiotonin*.³ Angiotonin has been isolated in crystalline form; it is heat stable and dialyzable. The hypertensive action of renin becomes less pronounced with successive injections. This tolerance to repeated injections of renin has been termed *tachyphylaxis*. The phenomenon is attributed by Page and his associates to the exhaustion of angiotonin precursor. The serum globulin (angiotonin precursor) is in low concentration in the plasma and is produced, apparently, in the liver since it disappears from the blood after hepatectomy. It is said to be increased in experimental hypertension and in clinical essential hypertension. Angiotonin exerts its constrictor action directly upon the minute systemic vessels. It reduces the renal

blood flow as a result, presumably, of constriction of the efferent glomerular vessels, which leads in turn to an increased filtration rate (p. 387). It does not increase the cardiac output.

Bing and Zucker believe that a pressor substance other than renin, namely, *hydroxytyramine*, is formed in the acutely ischemic kidney by the decarboxylation of l-dihydroxyphenylalanine. This latter, or l-dopa—as it is briefly designated—has no hypertensive action itself but when perfused through the excised ischemic kidney, but not through one with an adequate blood supply, forms the pressor amine *hydroxytyramine*. Also, when l-dopa is injected into the substance of a kidney rendered completely ischemic by clamping its pedicle and the clamp then released, a rise in blood pressure (of from 15 to 115 mm. Hg) occurs 3 hours or so later. On the other hand, when the circulation is restored to a completely ischemic kidney that has *not* been injected with l-dopa no rise in blood pressure occurs, unless the period of circulatory arrest is much longer than that cited in the previous experiment. The effect of *tyrosinase*—a phenolic oxidase—lends support to the idea just outlined of a pressor amine being the responsible agent in renal hypertension. This enzyme, as shown by Schroeder and Adams, lowers the blood pressure of animals suffering from the hypertension caused by renal ischemia and has the power to inactivate renin, adrenaline and tyramine *in vitro*. An amino-oxidase has also been prepared from hog liver, which, according to Schroeder, lowers the blood pressure of hypertensive patients and of dogs.

Raska has compared the enzymatic activity of slices of ischemic kidney tissue from hypertensive dogs with that of normal kidney tissue. The oxygen consumption of the ischemic tissue was found to be much below normal. Extracts were also prepared from ischemic kidneys and tested for their enzymatic activity (amino-acid oxidase, amine oxidase, and polyphenol oxidase activity) by measuring the oxygen consumption and ammonia production when tyramine, iso-amylamine, *dl*-alanine and *l*-aspartic acid were used as substrates. The activity of such extracts was found to be considerably less than that of extracts of normal kidneys.

Certain amino-acids after decarboxylation without deamination (p. 507) yield powerful pressor amines. An amino-acid carboxylase which acts under anaerobic conditions has been demonstrated in the kidney by Holtz and his associates. This observation combined with Raska's results and those of Bing and Zucker suggest that excessive amounts of pressor amines may be produced by the ischemic kidney as a result of an increase of anaerobic carboxylase activity and depression of oxidative enzymatic processes, and that such may be responsible, in part, for the hypertension following constriction of the renal artery. But there are several reasons for believing that they do not play a primary or dominant rôle either in experimental hyper-

³ Braun-Menendez and his associates have given the name *hypertensin* to the vasoconstrictor substance formed by the enzymatic action of renin upon the globulin of the serum, which they call *hypertensin precursor*. Hypertensin, therefore, corresponds to angiotonin and hypertensin precursor, to angiotonin precursor.

tension or in clinical essential hypertension. Among the observations which may be cited in argument against pressor amines playing an important part in the development of hypertension are, that the ischemic kidney does not suffer from anoxia and that decarboxylase is absent from the kidney of the rat, an animal in which renal hypertension is readily produced.

THE SOURCE OF RENIN AND THE ADEQUATE STIMULUS FOR ITS LIBERATION. Renin is confined to the cortex of the kidney. It is produced, or stored, apparently, by the proximal convoluted tubules and not by the juxtaglomerular (p. 379) apparatus as was previously supposed. Kidneys, in which the cells of the proximal convoluted tubules have been destroyed by poisoning with tartrate do not contain renin.

The stimulus for the production or liberation of renin by the kidney is not known. Ischemia does not appear to be directly responsible, for the immediate effect of constriction of the renal artery is dilatation of the renal vessels, the normal blood flow through the kidney being maintained. Anoxia of the renal tissue does not appear to be a necessary condition for the development of renal hypertension, because no increase over the normal occurs in the arterio-venous oxygen difference of the ischemic kidney (Levy and associates). On the other hand, anoxia induced by cyanide does not cause renin to appear in the circulation although a kidney so poisoned produces renin when the renal artery is clamped. Corcoran and Page, and Kohlstadt and Page believe that *reduction in pulse pressure in the renal vessels is the adequate stimulus*. They constricted the artery of a perfused kidney while normal blood flow and mean blood pressure in the vessels distal to the constriction were maintained. A reduction in pulse pressure in the renal artery distal to the constricting clamp was followed by the appearance of renin in the renal vein. Reduction in renal blood flow occurred only as a late effect.

It has been mentioned that ischemia of one kidney without interference with the kidney of the opposite side is not followed by permanent hypertension nor is the elevation of blood pressure, even while it lasts, as great if a normal kidney is present, and the return of the blood pressure to normal after excision of an ischemic kidney is much less rapid if the opposite kidney is also removed. Also, in order to demonstrate the maximum effect of the pressor substance liberated by the ischemic kidney the recipient animal must first be nephrectomized. All these facts suggested that normal

renal tissue elaborated a substance inhibiting the action of the pressor agent.

Braun-Menendez and his associates demonstrated the presence in normal kidney tissue of an enzyme which inactivates the pressor principle (angiotonin). This enzyme called *angiotonase* by Page and *hypertensinase* by its discoverers, is possibly responsible for the effect exerted by normal kidney tissue upon the development and severity of renal hypertension. Attempts to obtain a material from extracts of normal kidney tissue which would neutralize or inactivate the pressor substance responsible for clinical hypertension have not been very successful. Nevertheless, such an agent has been prepared by Grollman, Harrison and Williams and by Page and his associates which is stated to cause a pronounced amelioration of the hypertension due to renal ischemia, but is without effect upon the normal blood pressure or upon hypertension due to other causes.

THE ENDOCRINES IN RELATION TO EXPERIMENTAL HYPERTENSION. Though the evidence points to the hypertensive substance as acting directly upon the vessels, the possibility must be considered that it exerts its effect by stimulating a ductless gland, such as the pituitary or adrenal, to secrete a vasoconstrictor substance. That the adrenal medulla plays a rôle in this respect can be summarily dismissed, for the hypertension is not prevented or modified in any way by bilateral excision of all medullary tissue. On the other hand, Goldblatt has found that constriction of the renal arteries fails to cause a rise in blood pressure after bilateral removal of the adrenal cortex, even though the animal is maintained in good condition by a high salt and low potassium diet (p. 694). But if cortin is administered to the adrenalectomized animals, renal ischemia is followed by the usual hypertensive response. The blood pressure of hypertensive rats is lowered by adrenalectomy and is only partially restored by the administration of *desoxycorticosterone*. However, these results should not be taken to imply that the renal principle mediates its action *through* the adrenal cortex, for Houssay and his colleagues found that in short term experiments in which an ischemic kidney was transplanted into a non-hypertensive animal, complete adrenalectomy of the latter or ligation of the adrenal veins did not prevent the rise in blood pressure. These two sets of experimental results have been reconciled by the observation that angiotonin precursor is reduced after adrenalectomy. The cortical hormone appears to

be necessary, therefore, for the production of the substrate upon which renin acts. There is no evidence of the pituitary playing a rôle in the production of renal hypertension. So far as is known, the thyroid is not implicated in any way in its development.

THE SIGNIFICANCE OF THE RESULTS OF RENAL ISCHEMIA IN EXPERIMENTAL ANIMALS TO THE HYPERTENSION OF CHRONIC RENAL DISEASE. The immense importance of the experimental work which has been outlined in the foregoing sections and its bearing upon the hypertension secondary to renal disease requires no emphasis. Direct proof that reduction in the renal blood flow is the cause of the clinical condition and that a vasoconstrictor substance is elaborated in the diseased kidney as in the ischemic kidney of experimental animals is, of course, very difficult to obtain. But the experimental results are so clear cut that one is forced to the belief that the mechanisms in the experimental and clinical conditions are fundamentally the same. In chronic nephritis the vascular changes within the kidney undoubtedly can reduce the renal blood flow as effectively as compression of the renal artery. The increased peripheral resistance in chronic nephritis appears also to be of non-nervous origin. Pickering comes to this conclusion from his observations upon the cutaneous blood flow of patients. He found that in those with chronic nephritis and hypertension, warming the body (which inhibits vasoconstrictor tone of nervous origin) causes an increase in the blood flow through the hands, as determined by Stewart's method (p. 149), to a degree which falls far short of expectation were vasoconstrictor impulses alone responsible—an indication that some abnormal vasoconstrictor influence persists. Several clinical observations can be cited which stress the cogent argument offered by the experimental results in explaining the hypertension of renal disease. For example, in unilateral renal lesions, e.g., pyelonephritis, associated with hypertension, removal of the diseased organ is followed by the rapid return of the blood pressure to normal levels.

The experiments also carry important physiological implications or at least bring up some interesting questions. Does the pressor substance serve as a physiological mediator of renal blood flow? Is it in the nature of a humor or hormone liberated from the renal cells or produced by them when the functional demands upon the kidney call for a greater blood flow through its vessels? A rôle of this nature is suggested by an experiment performed by Drury. A loop of silk

thread slightly larger than the renal artery was tied around the vessel of one side in young, growing rabbits. As the animals grew the renal artery increased in size until it reached the diameter of the loop which from then on prevented the renal blood flow from increasing to meet the demands of the growing body. The opposite kidney made up for the deficiency by enlarging enormously and as long as it remained undisturbed the blood pressure did not rise. But removal of the hypertrophied kidney was followed by hypertension (up to 200 mm. Hg). An observation reported by Dill and Erickson points in the same direction, namely, that the vasopressor substance serves to proportion the blood flow through the kidney to the demands made upon renal function. The renal arteries on both sides were moderately compressed in a series of pregnant dogs. The operation was followed in from 48 to 120 hours by hypertension, nitrogen retention and hematuria. The animals had convulsive seizures and died in from 3 to 15 days in coma. Lesions in the liver, e.g., periportal necrosis, similar to those found in eclampsia were found at autopsy. Non-pregnant dogs whose kidneys were subjected to the same degree of ischemia, though they developed hypertension, remained in good health.

Hypertension occurs in *acute nephritis*, but the investigations of Pickering indicate that the mechanism of its production is not the same as in chronic nephritis. In the former disease vasoconstriction is apparently of nervous origin, for anesthetization of the ulnar nerve increased markedly the blood flow through the hand, leaving no abnormal vasoconstrictor influence. The hypertension of acute nephritis produced in rabbits by injections of sodium oxalate is also apparently of nervous origin, for Arnott and Kellar found that it is prevented by denervation of the kidney.

(2) *Primary, benign or essential hypertension (hyperpiesia)*

The immediate cause of the raised pressure in this as in the preceding type is an increase in the peripheral resistance, i.e., vasoconstriction or narrowing in some way of the peripheral vessels. It is not due to an increase in any of the other factors upon which the maintenance of the normal blood pressure depends, namely, the output of the heart, the viscosity⁴ or the volume of the blood. The calibers of the retinal arterioles are greatly nar-

⁴ A moderate increase in blood viscosity has been demonstrated in hypertension but it is a contributory cause and probably secondary rather than basic.

rowed, appearing upon ophthalmoscopic examination like silver wires. The state of these vessels may be taken as representative of that of the cerebral vessels and probably of the state of the peripheral vessels generally throughout the body.

The systolic and diastolic pressures are elevated equally, or the systolic to a greater degree than the diastolic; 250 mm. is not an unusual figure for the former and 130 mm. for the latter. In other cases, usually those in an advanced stage, the diastolic pressure is proportionately greater than the systolic, and the pulse pressure reduced. The pressure in the pulmonary circuit is believed to be normal. The pressure of the cerebrospinal fluid is increased in proportion to the rise in the diastolic pressure.

The pressure in the capillaries and small veins is within normal limits, and the slope of pressure through these vessels is not materially different from that in health. But the fall in pressure through the arterioles is much greater than in health (fig. 45). Ellis and Weiss found mean pressures of 155 and 12 mm. respectively in the brachial artery and in the capillaries—a fall of over 140 mm. Of this about 125 mm. must have occurred in the arterioles. Normally the fall of pressure in the latter vessels is about half this figure (approximately 60 mm.).

The high pressure in the arterial system, which of course must be overcome by the left ventricle before it can expel its contents, increases the work of the heart by from 40 to 50 per cent. The ventricular cavity becomes dilated and its walls hypertrophied. The cardiac output, except when the circulation is failing, is normal or only slightly reduced. In certain instances, according to some observers, it is increased. The vascular system, including the renal arterioles, in time suffers degenerative changes (p. 135) and renal insufficiency may then result (p. 402); a small contracted kidney is found after death. It should be emphasized that (as first pointed out by Albutt) the hypertension *develops* in the absence of demonstrable kidney disease. The latter when it occurs is the result of the hypertension. In other words, kidney disease is not a forerunner of essential hypertension but a sequel to it.

PATHOGENESIS. The cause of the *increased peripheral resistance* is unknown, though many theories have been proposed.

The pressure is lowered temporarily by drugs which cause vasodilatation, such as histamine; in a number of hypertensive cases examined by Ellis and Weiss the arteriolar resistance was, as in

normal persons, removed by this drug. These facts indicate that the vasoconstriction is largely due to spasm (fig. 45).

(1) *Nervous influences.* It has been suggested that the essential cause of the increased peripheral resistance is an inherent hypersensitivity of the vasoconstrictor nerves and an exaggeration of the usual vasomotor responses. The demonstration of an hereditary susceptibility to hypertension which is said to be a *dominant* characteristic and transmitted according to Mendelian laws has been pointed to in support of the latter view. Also Lord Dawson in the examination of 650 school children found the blood pressure well above the

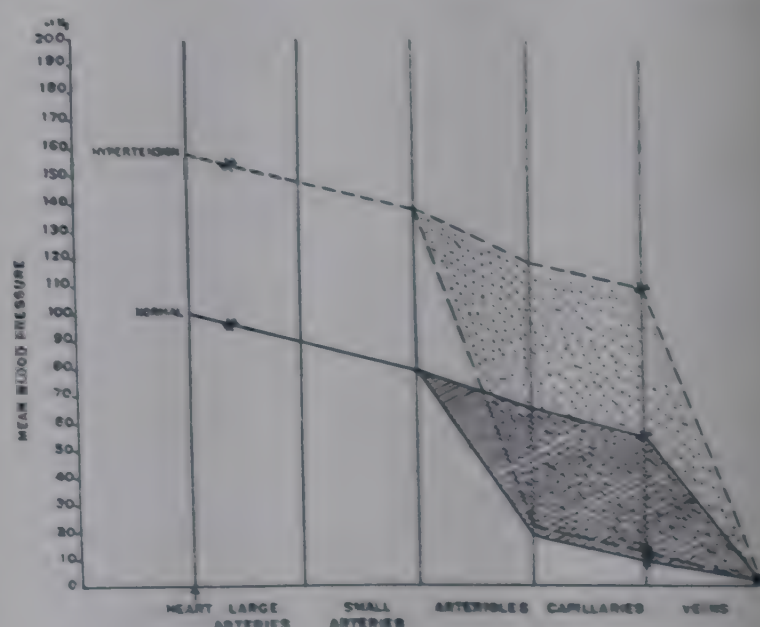


FIG. 45. Diagrammatic representation of fall in blood pressure in vascular circuit in subjects with hypertension compared with the normal. Shaded and stippled areas represent alteration in the pressure relationships in the skin vessels after the injection of histamine. The lower boundaries of these areas represent the pressure gradient under natural conditions; the upper boundaries this gradient after the injection of histamine (after Ellis and Weiss).

normal in 8 per cent. Hypertension has also been reported in infants.

In certain persons the response of the vasoconstrictor mechanisms to a cold stimulus—the so-called *cold pressor reaction*—is excessive. Hypertensive subjects commonly show a greater rise in blood pressure when a hand is immersed in ice water than do persons with a normal blood pressure (Hines). The cold pressor reaction also varies considerably among normal subjects. Those who respond to the cold test by a rise greater than 20 mm. Hg systolic and 15 mm. Hg diastolic are classed as hyper-reactors and are believed to possess a hypersensitive vasomotor system which renders them especially liable to

development of essential hypertension at some late date.

Though hypertension, temporary at least, may be produced in animals by denervation of the carotid sinuses (p. 244) and section of the aortic nerves there is no evidence that these mechanisms are directly concerned in the production of hypertension in man. The response of the carotid sinus to manual pressure (depressor response) is often actually more active in subjects of hypertension than in normal persons. Furthermore, in a study made by Thomas of the hypertensive effect of sectioning the sinus and aortic nerves in dogs, it was found that hypertension caused in this way differs from essential or renal hypertension in that increased cardiac output is an important factor in its production.

The nervous and emotional strain of modern civilization has frequently been pointed to as the underlying factor in the development of hypertension. There is little evidence which can be cited in support of the idea that mental strain, in the great majority of cases at any rate, is an important factor. In an analysis of some 30,000 applicants for life insurance Weiss found the average blood pressure no higher in medical men, teachers, lawyers, business men and others than in farmers who undoubtedly lead a life of greater mental calm. It should be mentioned, however, in this connection that Armstrong found in Air Force applicants a high correlation between hypertension and emotional instability, as determined by psychological examination. This finding applies, of course, only to healthy young men and not necessarily to women or to males of other ages.

(2) *Arteriosclerosis*. Ordinary senile arteriosclerosis which involves the larger and medium sized arteries does not cause hypertension. Some authorities have expressed the view that diffuse sclerotic changes in the systemic arterioles (p. 719) precedes the hypertensive state. On the other hand there is no doubt that such changes occur as a secondary effect of the strain upon the vascular tree induced by the heightened pressure. For this reason the question is a difficult one to answer definitely, yet obviously the finding of structural changes in the peripheral vessels cannot be taken as evidence that such changes are the primary cause of the hypertension and not secondary. It is conceivable, as Starling suggested, that obliterative vascular changes in the medulla would, by reducing the blood flow through the vasomotor center, (p. 292) cause hypertension. The possibility that

the latter is produced in this way in some instances cannot be ignored, but it is certainly true that such changes play no rôle in the great majority of cases.

The following experiments and observations indicate that excessive strain is a potent factor in the production of degenerative arterial changes. Josué and others have produced arteriosclerosis in rabbits by adrenaline injections. Sclerosis has also been induced in rabbits by placing them in the erect posture for a few minutes daily and so increasing the strain upon the arterial walls through the gravity effect. The sclerosis of the pulmonary artery which accompanies mitral stenosis is believed to be a result of the heightened pressure in the pulmonary circuit. Again, the removal of a section of artery and its replacement by a portion of vein is followed by sclerotic changes in the latter which are ascribed to the higher arterial pressure acting upon vascular tissue unsuited to withstand it; in aortic regurgitation the arteriosclerotic changes which occur are attributed to the constant buffetings to which the arterial walls are subjected by the high pulse pressure.

(3) *Toxic substances*. A great number of substances have been suggested as possible causes of the arteriolar changes responsible for hypertension. Among these are *cholesterol* which produces an elevation of the blood pressure in rabbits and arteriosclerotic changes. It has also been stated that subjects of hypertension have a high blood cholesterol. Critical investigations have failed to show, however, that this substance is causally related to hypertension. Pressor substances formed in the alimentary tract from the bacterial decomposition of protein, e.g. *tyramine* and *isocamylamine*, have also been suspected unjustly (see pp. 131 and 507). Lead, of all the toxic substances which have been suspected, appears to be the only one which in any way may be concerned with the development of hypertension. In lead poisoning the arterial pressure is elevated and degenerative changes are produced in the small vessels. Renal disease results.

(4) *The endocrines*. Excessive secretion of the *adrenal medulla* is not, except in those rare instances of adrenal adenoma (see p. 691), a factor in the production of hypertension. In *pituitary basophilism* (p. 737) (anterior lobe) hypertension does occur, through the hypertrophy or stimulation apparently of the adrenal medulla but there is no evidence that the anterior lobe or the hypertensive principle (pitressin) of the posterior lobe plays a rôle in ordinary essential hypertension. The same may be said of the *thyroid*. Though, as we have seen, hyperthyroidism may be accompanied by high blood pressure there is no evidence that the thyroid is concerned in the development of essential hypertension. If any substance, whether alimentary, metabolic or endocrine, in nature were responsible for the heightened blood pressure, one should expect that a pressor effect of the serum of subjects of hypertension could be demonstrated. Attempts to do so have failed.

Having in mind the experimental results of constriction of the renal artery in causing hypertension and the probability that renal ischemia is the cause of the high blood pressure in renal disease, the question immediately arises, "Is essential hypertension due to the same mechanism?" The hypertension in animals caused by a moderate degree of compression of the renal arteries (p. 129), with its relatively mild course and the absence of renal insufficiency, is comparable to "benign" hypertension in man; that caused by severe renal ischemia and accompanied by renal failure and widespread vascular damage resembles closely the malignant form of the human disease (see below). The observations of Moritz and Oldt may be cited in connection with the renal ischemia theory of essential hypertension. He has reported that in the histological examination of the kidneys of 100 hypertensive cases in which there had been no evidence of renal disease, arteriolar damage consisting of endothelial hyperplasia, medial hypertrophy and hyaline degeneration of the intima was an invariable finding. In the same number of kidneys from non-hypertensive cases, arteriolar disease was absent. So far as the systemic vessels were concerned, there was no corresponding distinction between hypertensives and non-hypertensives. These observations and those of others upon post-mortem material apparently indicated that either the walls of the kidney vessels are peculiarly susceptible to the hypertensive effect (i.e., that the renal vascular damage is secondary to the hypertension), which is unlikely, or that the arteriolar changes and the renal ischemia, consequent thereto, are the primary causes of high blood pressure. A more recent study by Castleman and Smithwick has failed, however, to support the renal ischemia theory of the origin of essential hypertension. The vascular changes in renal tissue removed at operation from hypertensive cases were not significantly greater than those found in the kidneys of persons with normal blood pressures.

Malignant hypertension

In this condition the hypertension is associated with wide spread degeneration and occlusion of the peripheral vessels. The media of the arterioles and small arteries show hypertrophy of their muscular tissue and fibrosis. Hyperplasia and degenerative changes are found in the intima. Small hemorrhages are commonly found in various regions due to the necrosis of the walls of the

vessels. As a result of the destruction of the glomeruli, renal failure ensues and death in uremia may occur. More usually death is by cerebral hemorrhage. This condition is probably of the same nature as the benign form but of a much more severe grade.

Eclampsia gravidarum

Eclampsia is accompanied usually by a very high blood pressure of rapid development. The diastolic pressure shows the more pronounced rise indicating a generalized vasoconstriction. The cause of the arteriolar spasm is unknown. The blood pressure, as a rule, falls after evacuation of the uterus, which fact together with other features of the eclamptic state suggests, that an abnormal metabolic product, or possibly an endocrine secretion, acting either upon the vasomotor center, or directly upon the vessels is responsible. Hyposecretion of the posterior lobe of the pituitary has been regarded as a possible cause. Anselmino and Hoffmann, for example, claim to have isolated a substance from the plasma of women in eclampsia which, when injected into rabbits, exerts an antidiuretic effect (p. 731), increases the concentration of urinary chlorides and raises the blood pressure. The convulsive seizures of the eclamptic state are attributed to the water retention (water intoxication, p. 19) consequent upon the antidiuretic effect of the hormone. This work has been confirmed. Theobald also obtained an antidiuretic principle from the blood of eclamptic cases but he denies its identity with that of the pituitary and Melville, who obtained a similar material from the blood in normal pregnancies, concludes that there is no causal relationship between the pituitary and eclampsia; other observers have come to the same conclusion. The possibility that the eclamptic state is due to a relative or functional ischemia of the kidney is suggested by the experiments already cited (p. 129). On the other hand, a pressor agent produced by chorionic tissue as a result of placental ischemia, may be responsible for the peripheral vasoconstriction and for the renal changes. Such a substance might act primarily upon the systemic and renal vessels causing hypertension, which in turn would lead to renal damage. Experiments have failed, however, to demonstrate a pressor substance in placental extracts either from normal or toxemic pregnancies.

HYPOTENSION

In an adult an arterial pressure which is persistently below 110 mm. Hg and for which no cause

be found is referred to as essential or primary hypotension. The subjects of essential hypotension, beyond showing possibly a greater susceptibility to fatigue, suffer no ill effects; on the contrary they are more likely to be free from cardiac and renal disease, the condition for this opinion being said to forecast longevity. Robinson says "Hypotension is not a disease; it is the ideal blood pressure level."

Apart from the foregoing type, low blood pressure occurs either as a temporary or a persistent phenomenon in many conditions. Some of these are hemorrhage, traumatic shock, anesthesia, tuberculosis and debilitating diseases of various kinds. It may occur also, as a result of the vasodilation and cardiac atrophy associated with acute fever; from myocardial failure; and in Addison's disease and in hypothyroidism.

Orthostatic hypotension is an unusual but interesting condition in which the reflex mechanisms normally operating to maintain the blood pressure against the effect of gravity are apparently in abeyance, or their sensitivity greatly depressed (p. 141). A profound fall in blood pressure occurs in the standing position; the systolic pressure may fall to 40 mm. Hg and the diastolic to zero (as determined by the usual method). The subject experiences dizziness or may fall in a faint. Other features of this condition are (a) absence of sweating, (b) failure of the pulse rate to increase upon rising from recumbency to the standing position, (c) slight depression of the basal metabolic rate, (d) loss of sexual desire, (e) skin pallor and (f) blood urea around the upper limit of normal. The inability to sweat, taken together with the failure of the reflex vasoconstriction to a change in posture, suggests some fundamental abnormality of the sympathetic nervous system. The administration of benzedrine sulphate effects some temporary relief by reducing the extent of the fall in blood pressure in the standing position.

VENOUS BLOOD FLOW

FACTORS WHICH INFLUENCE THE FLOW OF BLOOD IN THE VEINS

It has been mentioned (p. 117) that the blood pressure slopes gradually through the systemic capillaries and veins to the right auricle, but that with the narrowing of the venous bed from the "capillary lake" to the right side of the heart the velocity of flow increases. The following are the factors which influence the venous flow.

- (1) Contraction of the left ventricle.
- (2) The quantity of blood flowing through the arterioles from the arteries in relation to the capacity of the capillaries and veins.

(3) The subatmospheric pressure within the thorax.

(4) The action of the right side of the heart.

(5) The massaging effect of the skeletal muscles and the support afforded by the abdominal wall.

(6) The effect of gravity.

(1) *The contraction of the left ventricle* (the "vis a tergo"). The energy of the ventricular contraction as we have seen is expended in driving the blood through the arterioles and onward in the veins to the right auricle. By the time the blood reaches the auricle the energy has been almost entirely dissipated in overcoming the frictional resistance offered by the vascular channels; at this point the pressure is only about 5 mm. of water.

(2) *The quantity of blood flowing through the arterioles in relation to the capacity of the capillaries and veins.* Generally speaking, the more blood which is received from the arterial side the greater will be the capillary and venous pressures. That is, with dilated arterioles the difference between the arterial pressure on the one hand and capillary and venous pressures on the other, tends to be reduced; with constricted vessels the pressure difference will be increased. The relationship, however, does not always hold for the reason that the capillaries and veins are under nervous control (p. 250). As a consequence, the capacities of these vascular regions are capable of adjustment to the quantity of blood received from the arterial system. The capillaries and veins may dilate to accommodate the extra blood, so that little change in capillary or of venous pressure will result. Bayliss and Starling, for example, found that when the arterioles opened as a result of the stimulation of a vasodilator nerve (p. 233) the expected rise in venous pressure did not always occur, and Hooker observed that when the hands were warmed, more blood entered the veins but a rise in venous pressure did not result. On the other hand, if the arterioles constrict the capillaries and veins may, by an active contraction of their walls, reduce their capacities and thus maintain the pressure in spite of the reduced amount of blood which they receive.

(3) *Subatmospheric pressure within the thorax.* The intra-thoracic pressure has an important influence upon the flow of blood along the great veins of the thorax and abdomen and consequently upon the filling of the right auricle. During inspiration the pressure within the thorax is about -6 mm. of mercury (81 mm. H_2O) below that of the atmosphere. During expiration it amounts to about -2.5 mm. of mercury (34 mm. H_2O). The sub-

atmospheric pressure expands the thin-walled intra-thoracic veins and the venous blood is sucked into the thorax. A similar effect but of less degree is exerted upon the walls of the auricles, the diameters of the thick-walled ventricles, however, and the comparatively rigid coats of the larger arteries remain practically uninfluenced by the "negative pressure" during ordinary breathing. It has been mentioned that the blood in the great veins at their entrance into the auricle has a small but definite pressure of about 5 mm. H₂O transmitted from the arterial side. That is to say, if the thorax were opened so as to abolish the sub-atmospheric pressure within it and a manometer placed in the inferior vena cava a positive pressure of this magnitude would be registered.

The flow of blood toward the heart is thus furthered by both the positive pressure in the venous system and the suction pressure exerted by the thorax. The sum of these two is sometimes spoken of as the *effective venous pressure*. Thus, if the positive pressure in the great veins at the right auricle amounts to +5 mm. H₂O and the pressure within the thorax to -80 mm. then 85 mm. represents the effective venous pressure. Since the negative pressure in the thorax increases during inspiration, the effective venous pressure must likewise increase and auricular filling be hastened during this phase of respiration. The descent of the diaphragm during the inspiratory phase, also, by compressing the abdominal contents, increases the pressure in the inferior vena cava (the femoral veins and sometimes the iliacs being provided with valves) and augments the flow of blood toward the heart. The thorax thus acts as a pump which "lifts" the blood as well as "forces" it toward the heart (see fig. 131, p. 297). Sometimes when vigorous respiratory efforts are made, slight fluctuations of the venous pressure can be detected in the peripheral veins of the human subject. The variations rarely amount to more than 10 mm. of H₂O but may be considerably higher than this when dyspnea resulting from obstruction to the free entrance and egress of air from the lungs exists. Owing to the inertia of the blood column the aspirating effect is less evident the nearer to the periphery at which the pressure measurements are made.

The respiratory effects upon venous pressure can also be exaggerated in the normal subjects by the following procedures. If a forced expiration be made with the glottis closed (Valsalva's experiment) the negative intrathoracic pressure can be abolished and a positive pressure of several milli-

meters of mercury substituted. The veins of the neck, face and limbs become distended with blood as a result of the impediment to the flow into the right auricle. The peripheral venous pressure under these circumstances may rise to 400 mm. H₂O or more. In the converse experiment of Mueller in which a forced inspiration is made with the glottis closed, the powerful suction effect may cause a fall of 50 mm. H₂O or so in the venous pressure of a peripheral vein. The increase in negative intrathoracic pressure may be seen by means of the X-ray to exert an effect upon the ventricle which during diastole becomes somewhat enlarged beyond its usual size.

(4) *The action of the right side of the heart upon the blood-flow in the veins.* Obviously if the blood is not passed on again by the right heart as quickly as it is carried to it by the great veins, the velocity of the blood flow in the venous system will be reduced. As a result the venous pressure will rise. That is, there will be a tendency for the blood to be "dammed back." When the heart is beating vigorously and output and inflow are balanced no rise in venous pressure occurs. In health the force of the ventricular contraction is nicely adjusted (p. 215) to the quantity of blood which pours into the auricle from the veins and no accumulation occurs. If, however, the heart fails the venous pressure rises and back pressure effects ensue (p. 222).

The influence of cardiac action upon the movement of the blood in the veins must not be taken to imply that the heart exerts any aspirating effect. The ventricle does not "draw" blood from the auricle and great veins when it relaxes and expands as one would suck up fluid by means of a bulb-syringe. Such an action has been suggested but it is difficult to conceive how any significant effect of this nature could result even were a negative pressure appreciably below that within the thorax created within the heart chambers. The veins are thin walled and any reduction of pressure upon their outer surfaces, as we have seen, causes them to expand. But a lowering of pressure in their interiors would cause them to collapse, and the venous flow would be blocked automatically before the inertia of the blood had been overcome. Moreover, intra-ventricular pressure curves fail to show a negative pressure during cardiac relaxation (fig. 64) as might be expected if the ventricle exerted a suction effect upon the blood in the great veins.

It may be mentioned, however, that during *systole* the ventricle does cause a slight fall in pressure in the auricle and in the great veins due to the drawing down of the floor of the auricle (p. 170). Also as a result of the ejection of 60 cc. or so of blood from the thorax at

each beat a slight but sharp increase in the negative pressure within the thorax is induced during the cardiac contraction. This is reflected in the veins, auricles and other thin-walled intrathoracic structures. It may even be detected within the thoracic portion of the oesophagus by placing a balloon therein and recording the pressure change. These variations in intrathoracic pressure occurring during the contraction of the ventricle are known as the negative heart pulse or the cardio-pneumatic movements.

(5) *The massaging effect of the muscles.* The intermittent pressure which is brought to bear upon the blood by contraction of the limb muscles aids in propelling it towards the heart. The arrangement of the valves of the veins serves to give the blood flow this direction. The muscles thus act as subsidiary pumps which aid very materially the flow of venous blood, especially during muscular exercise, but to a lesser extent at all times, except when there is complete muscular relaxation. In strenuous exercise, on account of the much greater amount of blood entering the veins from the arterial side, there is a tendency for the venous pressure to rise; but this to a large extent is compensated for, provided the cardiac action is unimpaired, by the increased aspirating effect of the respiratory movements. The muscles of the abdominal wall also contract during exercise to lend support to the abdominal veins and prevent them from becoming over-distended. The venous reservoir is in this way not permitted to enlarge its capacity unduly for the accommodation of the increased volume of blood which, in consequence, is borne onwards to the right auricle.

(6) *The effect of gravity.* Besides the hydrodynamic factor, i.e., the energy of the cardiac contraction, in the development of pressure within the vascular system, there must also be considered the hydrostatic factor, or weight of the blood column, which comes into play when the erect posture is assumed. It is convenient to consider the arterial and venous systems together in their relation to the hydrostatic effect. Above the level of the heart gravity opposes the hydrodynamic factor in the arteries but aids it in the veins. Below heart level the reverse is true, the hydrostatic and hydrodynamic factors being summed in the arteries but opposed to one another in the veins.

In the case of the *arteries* the effect of gravity upon the blood in the vessels above heart level is fully compensated. That is, the pressure in the brachial artery is as high or actually higher when the subject is standing than when he is lying down. The pressures in the brachial and femoral arteries

are approximately equal in the latter position. Unlike the brachial pressure, the pressure in the arteries of the lower limb varies widely with the position of the body. When the subject is in the vertical head down position or in the L position (lying on back with lower limbs vertical) the pressure in the artery of the leg is much lower than it is in the recumbent position. In the standing position, on the other hand, the pressure in the leg artery is higher than in the lying down position (lower limbs horizontal); owing to the hydrostatic effect, the nearer the foot that the measurement is made the higher will be the observed pressure. The difference between the pressures in the brachial and the artery of the leg in these different positions is equal to the height of a blood column which would reach from one artery level to the other. In the case of the blood supply to the upper part of the body nervous mechanisms (p. 231) governing the caliber of the arterioles (especially of the splanchnic area) are called into play to antagonize the gravity effect. An adequate pressure in the cerebral vessels is thereby assured; but there is no corresponding mechanism for the maintenance of a constant blood pressure to the lower limbs, nor, in the natural positions of the body, is it required. The pressures in the brachial and posterior tibial arteries in different positions of the body are given in table 14.

Though the systolic pressures in the femoral and brachial arteries are usually about equal in the horizontal position, a marked difference between the two is seen in aortic regurgitation, the femoral systolic pressure averaging some 50 mm. Hg higher than the brachial pressure (L. Hill and Rowlands). A "differential" pressure of this character is also observed in exophthalmic goiter (average 37 mm. Hg higher in femoral) and in arteriosclerosis (average 8 mm. higher in femoral). It may also be seen in normal persons after muscular exercise. The differential pressure is attributed by Bazett to the greater resistance offered to the flow of blood in the femoral artery and the conversion, in consequence, of a greater proportion of kinetic energy into stress as the blood stream is slowed. The greater mass of the blood column entering the femoral artery as compared with that entering the brachial is also a factor.

It is through the *venous system* that the effects of gravity upon the circulation are the more prominently displayed. This is on account of the lower venous pressure, the greater distensibility of the venous walls, and also of the fact that the

height of the blood column which must be raised against gravity is much greater (from feet to heart) than that of the arterial blood column (from heart to brain). In man the mechanisms whereby the effects of gravity upon the venous system are offset are remarkably efficient. In monkeys also, the compensatory devices are well developed and in some varieties of these and in the anthropoid apes the effect of gravity is counteracted as effectively as in the human subject. In many of the lower animals, on the contrary, there is little evidence of compensatory mechanisms.

The factors which enable the blood in the veins below the thorax to overcome the gravity effect and to be carried to the level of the auricle are several. Let us consider for a moment a U-shaped tube with rigid walls. If liquid be permitted to flow into one limb of such a tube, the liquid, being

concerned with raising the blood against gravity may be given again here. They are:—

(a) The impetus given to the blood by the left ventricular contraction (*vis a tergo*).

(b) The abdominal and limb muscles support the vein walls and prevent their “giving” under the weight of blood. By this means the veins in a sense come to simulate rigid tubes. When the abdominal muscles are weakened or paralyzed the support which they normally provide is seriously impaired, but may to a large extent be restored by a tight abdominal bandage. The intermittent contraction of the skeletal muscles which in conjunction with the valves of the veins propel the blood in the upward direction. The important part played by the muscles in the return of blood to the heart is shown by experiments in which the body is passively tilted into the upright position.

TABLE 14
Showing effect of gravity upon the arterial blood pressure
(Modified from Hill and Flack)

POSTURE	BRACHIAL ARTERY PRESSURE	POSTERIOR TIBIAL PRESSURE	PRESSURE DIFFERENCES OBSERVED	PRESSURE DIFFERENCES CALCULATED FROM HEIGHTS OF BLOOD COLUMNS SEPARATING POINTS IN TWO ARTERIES
	mm. Hg	mm. Hg	mm. Hg	mm. Hg
Horizontal	106	106	0	0
Standing	110	165	55	58
Vertical, head down	115	50	65	65
L position, legs up	115	85	30	33

supported by the rigid walls, rises in the other limb until it overflows. After the liquid has been allowed to come to rest, then at any level of the tubing, the hydrostatic pressure corresponds to the height of the liquid column extending above that level. The aorta with the main arteries of the lower limb, and the inferior vena cava with its tributaries, are roughly comparable to two limbs of a U-tube. But the venous walls are highly distensible and quite incapable of supporting the blood column, and, unless the gravity effects were overcome, the blood would sink and “find its own level.” Furthermore, a system of small vessels—capillaries and venules—of variable capacity is interposed between the limbs of the U. In the corpse, for example, the blood subsides to the dependent parts, and the hydrostatic pressure when the body is held erect amounts to no more than a few centimeters of water.

Though the factors which aid the venous flow have already been dealt with, those especially

Persons who fail to show a rise in intramuscular pressure when tilted passively are likely to faint.

(c) The suction and force-pump action of the respiratory movements.

(d) The veno-pressor and capillary tonus mechanisms which, through the activity of the sinus and aortic nerves (p. 240), control the calibers of the small veno-capillary vessels of the splanchnic bed and prevent pooling of blood in this area.

If any or several of these factors fail, accumulation of blood (venous stasis) in the dependent parts of the body is likely to result. Thus, in the human subject if, upon assuming the erect posture after a protracted confinement to bed, the muscles of the abdomen and limbs are weak and the tone of the nervous mechanism governing the peripheral vessels lowered, the hydrostatic effect is overcome with difficulty. The blood subsides into the capacious abdominal veins and capillaries and the right heart is no longer adequately supplied with blood. The blood supply to the brain is reduced, with

diness (vertigo) or loss of consciousness (syncope) as a result. A sudden drop of about 25 mm. Hg is usually sufficient to cause unconsciousness. Even a healthy man may faint if kept standing and immovable in one position for a long period (e.g., a soldier standing to attention on parade). The blood is not driven upwards in the usual manner by the massaging effect of muscular movement. The failure of the right heart to receive an adequate blood supply to maintain the cerebral blood pressure affords a probable explanation of the syncope that occurs under these circumstances. It is an interesting reflection in this connection that when a person falls to the ground unconscious the horizontal position annuls automatically the effect of gravity. The head-low position and pressure upon the abdomen are obviously the most effective means of getting the blood to the heart and so restoring the circulation. On the other hand, if a person were held in the upright position after unconsciousness had been lost death might result, just as a domestic rabbit succumbs when held for a much shorter time in the head-up-feet-down position. Under chloroform and to a less extent under ether and other anesthetics, in shock and in various unconscious states the compensatory responses are depressed and any change from the horizontal position under these conditions is therefore fraught with serious danger to life. Certain vasodilator drugs and sodium nitrite (p. 254) annul the compensatory response, and it is relatively insensitive in severe arteriosclerosis (see also orthostatic hypotension, p. 136). That compensation is not perfect even in health is shown by the slight reduction in cardiac output (p. 226) which occurs in the standing position. Also, though an increase in blood volume results from a rise in environmental temperature, the compensatory vasoconstrictor response to a change from recumbency to the upright position is reduced by a rise in air temperature.

The effect of gravity upon the circulation in an animal such as the dog or cat which normally is fairly well able to compensate for postural changes, and the importance of the various factors comprising the control mechanism have been well shown by L. Hill. The medullary control over the peripheral vessels was removed by section of the cord at the level of the 1st thoracic vertebra. The tone of the abdominal muscles is also lost after this operation and the respirations are altered. The blood pressure falls even when the animal is in the horizontal position. When placed in the feet-down position, the pressure drops to zero. If the animal's abdomen be compressed the capacity of the

splanchnic vessels is thereby reduced and blood forced upwards to fill the right heart. The blood pressure is raised again and the circulation restored. In the head-down, feet-up position the rigid cranial wall supports the blood column, the heart fills and the carotid pressure rises. When the main nerve trunks (splanchnics, p. 940) carrying fibers to the peripheral vessels are divided alone the respiratory pump in part compensates for the gravity effect, and though marked changes in pressure occur when different positions are assumed the circulation is maintained. Edholm found that the blood pressure of normal cats under chloralose anesthesia fell by 34 mm. Hg on the average when the

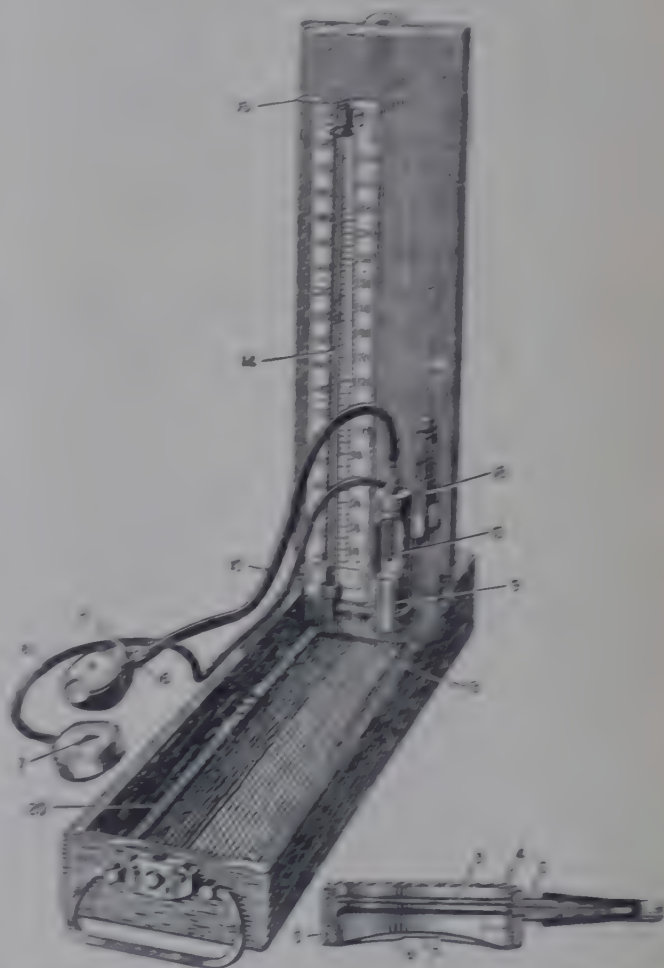


FIG. 46. Apparatus for the determination of venous blood pressure in man by the indirect method. For detailed description of parts see "Clinical measurement of venous pressure." Eyster. Macmillan. 1929.

animal was held in the vertical feet-down position, but recovered shortly to a final pressure within 30 mm. Hg of its previous level in the horizontal position. It appears from Edholm's results that pooling of blood under the effect of gravity occurs in the liver and not to any great extent in the splanchnic vessels generally, for the fall in blood pressure in the feet-down position was about the same after evisceration as before, whereas, after removal of the liver from eviscerated animals, the vertical feet-down position caused a fall in blood pressure of only from 5 to 10 mm. Hg. That the splanchnic vascular bed is, nevertheless, a factor in the compensatory mechanism tending to oppose the effect of gravity was indicated by the observation that the

final height of the blood pressure in the foot-down position was higher in normal than in eviscerated animals.

The circulation of animals such as the domestic rabbit or the snake, which have not acquired a compensatory mechanism, is placed at a great disadvantage when the vertical position is assumed.¹ This has been shown very clearly upon the latter species in the following experiment. The heart and abdominal vessels were exposed and the reptile fastened to a board. The right side of the heart was seen to be adequately supplied with blood so long as it was held in the horizontal position. When placed vertically the auricle was no longer properly filled and the great veins entering the heart were nearly empty. When the preparation was then immersed in a cylinder of water up to the heart level the hydrostatic pressure of the venous blood was counterbalanced by that of the surrounding water, and the blood again flowed freely into the heart chambers.

THE CLINICAL MEASUREMENT OF THE VENOUS PRESSURE

Hooker and Eyster have devised an instrument for the *indirect measurement* of the venous pressure based upon the principle first employed by von Recklinghausen.

In its present improved form the instrument consists of a small round chamber with a glass top and metal walls (fig. 46). Over the bottom of the chamber is stretched a piece of rubber dam with an opening about half an inch square in its center. Lengths of rubber tubing connect the cavity of the chamber, respectively, with a water manometer and a small hand bulb. The rubber dam is moistened with glycerine and placed with its central opening lying over the vein to be examined. The pressure within the chamber is raised by a few compressions of the bulb. The venous pressure will equal that required to cause collapse of the vein. This pressure is read from the manometer at the instant that collapse occurs. All determinations are made with the vein at the level of the auricle so as to annul the hydrostatic effect. The part is supported in order to ensure complete muscular relaxation and the subject should be at rest for 15 minutes prior to the determination. If the pressure is measured with the subject recumbent, the vein, e.g., median basilic or a vein of the forearm or hand, is placed at a point situated one-third of the distance from the sternum to the back at a level of the 4th intercostal space. If the measurement is made in the sitting position the vein is brought to the level of the 4th interspace.

The venous pressure may also be determined *directly* though less conveniently and with more discomfort to the subject but no more accurately by the insertion into the vein of a hollow wide-bore needle, as first employed by Moritz and von Tabora.

¹ Sheep sometimes collapse and die when held upright during bleeding.

A simple indirect method which gives approximate results is that of Gaertner. With the patient in the supine position the hand is first lowered below heart level until the veins on the back of the hand fill. The part is then slowly raised until the veins collapse. The distance of the vein in millimeters above the auricle at which collapse occurs gives the venous pressure in millimeters of blood. The vein represents a manometer tube connected with the auricle and the level at which the vein empties indicates the point where the venous pressure at the auricle just about equals the weight of the blood column.

NORMAL VENOUS PRESSURES

The pressure in the median basilic vein taken with the body recumbent shows considerable variations in different individuals. The range is between 40 and 110 mm. H₂O. The pressure is greater in veins nearer the periphery and shows a progressive diminution toward the heart. It must be remembered that the pressure as measured is the algebraic sum of the positive pressure transmitted from the arterial side and the negative pressure exerted upon the blood column from the thoracic cavity. The effect of the latter is slight in the peripheral veins, but as the thorax is approached the venous blood comes decidedly under its influence. According to Burton-Ogata the decline in pressure along the peripheral veins amounts to 1 mm. Hg (13.5 mm. H₂O) for each 35 mm. distance. The point of zero pressure i.e., where negative and positive pressures just balance one another, is in the case of the upper part of the body, in the jugular vein at the root of the neck below this point the pressure is negative.² As

² For this reason there is supposed to be danger should a vein be nicked in this region during an operation, air being sucked in, and carried to the heart. The air might then be shipped up with the blood and cause frothing within the cardiac chambers, with resulting acute cardiac failure or pulmonary embolism, or even reach the arterial system and cause blockage of a cerebral vessel. The fear of air entering the vein under such circumstances, however, would appear to be exaggerated. The walls of the vein collapse under the suction pressure within and appose one another close the lumen. Furthermore, even should a small amount of air enter the vein, it is unlikely that serious effects would ensue, since to produce the effects just described in an animal relatively large quantities of air must be injected. Dukes, Richardson and Hall have observed from their experiments upon dogs that about 500 cc. of air in the circulation would be lethal for a human being. A more likely portal for the entrance of air into the circulation is via the uterine veins during the induction of abortion or blowing labor at term. Several fatalities supposedly due to this cause have been reported. It may also occur during the collection of air into the pleural cavity for the production of pneumothorax. It is probable, however, that in many instances in which death has been attributed to air embolism it has been due to some other cause.

ed above, it varies between -35 and 0 mm. H_2O at the right auricle.

Point of zero venous pressure below the heart at about the level of the entrance of the veins into the vena cava (Barton-Ostiz). Venous pressure varies, of course, as a result of gravity effect, with the position of the vein in relation to the auricle. In the veins of the hand, for example, the pressure is lower by from 50 to 100 mm. H_2O when the hand is at heart level than it is dependent. The differences in pressure arising from changes in the vein's level will obviously be larger in the case of the lower limbs. Since certain factors, already mentioned, enter into the gravity effect the actual differences as observed do not coincide with the height column of blood from the vein level to the heart.

The greater the velocity with which the blood flows upwards the greater will be the discrepancy between the calculated pressure and that actually measured (see also p. 114). For example, the hydrostatic pressure of a column of blood extending from the foot to the heart would amount to over 1200 mm. H_2O . The pressure as actually measured in the vein of the foot in the standing position is only a fraction of this. The effect of muscular exercise upon the venous pressure has been considered (p. 139). The relation of venous pressure to heart rate and cardiac output is discussed with on pages 209, 216, 224 and 227.

VARIATIONS IN VENOUS PRESSURE

Muscular Exercise causes a prompt rise in the pressure of blood in the veins of the exercised parts. **Constriction of a peripheral vein** will, of course, cause a local rise in venous pressure and compression of the large intrathoracic veins will be followed by a general rise.

Cardiac failure. As the right ventricle weakens and dilates, the pressure in the right auricle rises and is transmitted to the blood in the portal and systemic veins (see fig. 47). The pressure in the median basilic vein may reach a value of over 100 mm. H_2O . The increased pressure distends the veins and capillaries of the portal system; the liver becomes enlarged and the other abdominal organs engorged. The rise of pressure in the systemic veins and capillaries increases the filtration pressure, edema results. The slowing of the flow through the small vessels of the skin causes cyanosis. Both edema and cyanosis tend to be more pronounced in the dependent parts (feet and ankles). The rise in pressure in the veins results in slowing of the circulation

through the glomeruli, the urinary secretion is reduced. The rise in pressure in the cerebral veins leads to slowing of the intracranial circulation, especially when the patient is recumbent and the venous return from the head is, therefore, not aided by gravity. Failure of the left side of the heart causes a rise in pressure in the left auricle which is transmitted to the pulmonary circuit and ultimately to the right side (see also p. 222). The lung vessels distend and encroach upon the air spaces. With the improvement in cardiac



FIG. 47. Upper drawing, normal subject supine with head on pillows. The zero level (Z.L.), indicated by the top point of swelling of the external jugular vein, lies a little below the manubrial line (M.L.). Lower drawing, illustrating excessive venous pressure equivalent to about 8 cm. of water. In the upright position the zero level may be just a little above the clavicle, as the subject is inclined the zero level comes to occupy a higher and higher position in the neck until it reaches to the angle of the jaw. Its vertical distance above the manubrium alters very little, however, with changes in position (after Lewis).

action induced by rest and digitalis administration, the venous pressure falls.

In hypertension, except when myocardial failure is impending or has supervened, the venous pressure is within normal limits.

In the stage of excitement during the induction of anæsthesia a very considerable elevation of the venous pressure may occur. The effects of disturbances of the respiratory mechanism upon venous pressure are also seen in convulsive attacks (p. 368) and in Cheyne-Stokes breathing (p. 352). The pressure rises to 180 mm. H_2O or so during

the phases of apnea of the latter condition, but approaches the normal value during the periods of hyperpnea. Reduction in the carbon dioxide content of the blood, if extreme, lowers venous pressure by increasing the tone of the peripheral vessels.

In severe *hemorrhage* and *surgical shock* the venous pressure is subnormal.

THE EFFECTS OF ACCELERATION UPON THE CIRCULATION

A constant speed, however great, has in itself no effect upon the circulation. As pointed out by Armstrong, we are travelling through space quite unaware of a speed of over 18 miles per second caused by the motion of the earth. But acceleration, that is, a change in velocity either in the line of our motion (linear acceleration) or a change in direction, as when a body travelling along a straight course turns into a curvilinear one (centrifugal acceleration), may cause profound effects upon the body as a result of the inertia of the blood and viscera. The development of the modern airplane and the manoeuvres of military flying have brought prominently to the fore in recent years the importance and hazards of acceleration in relation to the circulation. According to Newton's Law, $F = MA$ where F = force, M the mass and A the linear acceleration. Therefore, $A = \frac{F}{M}$. That is

linear acceleration is proportional to force and inversely proportional to mass. Centrifugal acceleration depends upon the *rate* of change in direction and upon the velocity. It is expressed

by the formula $F = \frac{MV^2}{r}$ in which V is the velocity

and r the radius of rotation. Now, weight is a measure of the force of gravity and is proportional to mass. The force of gravity is used, therefore, as the unit of measurement of acceleration and is

denoted by the letter "G". Thus, an acceleration of 2 Gs indicates a force double that of gravity. Acceleration which produces a force acting upon the airman in the long axis of the body from head to seat is called positive (+G); that acting from seat to head is called negative (-G). A pilot pulling out of a power dive, that is, changing direction at high velocity to a horizontal and upward direction has his head directed inward toward the center of rotation and is therefore subjected to a positive centrifugal acceleration. If the force amounts to from 5 to 6+ G, or more, the phenomenon now generally referred to as "blackout" results, for the blood, owing to its inertia is "forced" into the lower part of the body (the large vessels, it will be recalled, run in the general direction of the long axis of the body). The venous return to the heart is reduced and, as a consequence, the pressure of blood in the cerebral and retinal vessels falls. Vision is temporarily lost and the pilot may become unconscious. The abdominal viscera are forced downwards and drawing upon the diaphragm may embarrass respiration.

Negative acceleration, as when a turn is made at high velocity in pulling up from horizontal flight, the pilot's head being directed outwards, causes opposite effects upon the circulation. Blood is forced toward the head. The vessels of the head and neck become engorged, there may be small cutaneous hemorrhages, severe throbbing pain in the head is experienced and the eyes feel as though they were being extruded from their sockets. The abdominal viscera are pushed upwards against the diaphragm. The venous return to the heart is increased and the blood pressure in the cerebral vessels is raised considerably (as much as 65 mm. Hg). There may be mental confusion for a time. Cerebral hemorrhage may result.

CHAPTER XVII

THE VELOCITY OF THE BLOOD

The relative blood velocities in different parts of the circulation are dependent upon the sectional areas of the respective vascular beds (see p. 119). The velocity of the blood through the circulation as a whole, on the other hand, varies in accordance with the quantity of blood ejected per unit of time from the heart.

The velocity of the blood may be considered from four different aspects which are indicated by the following terms:

- (a) The mean lineal velocity.
- (b) The circulation time.
- (c) The volume flow.
- (d) The circulation rate or output of the heart.

The output of the heart (d) will be dealt with later (Chapter XXVI). The other three measurements will be considered now.

(1) THE MEAN LINEAL VELOCITY

By this term is meant the distance which the column of blood travels in a measured period of time along a given vessel, e.g., the carotid, femoral, etc. In very small transparent vessels, for instance those of the mesentery of a mammal or those in the tongue or toe-web of a frog, the blood velocity can be measured by timing the progress of a red cell beneath the microscope. In the large vessels the velocity can be calculated if the quantity of blood which passes a given point in a unit of time and the cross area of the vessel are known. It is, of course, not permissible merely to sever an artery and measure the amount of blood which escapes over a certain period, since such a procedure would completely alter two of the most important factors in the circulation, namely, the total blood volume and the peripheral resistance. Several instruments have been devised for measuring the volume of the blood flow in animals while the normal circulation is maintained.

Of such instruments the *Stromuhr* of Ludwig is one of the oldest and the best known (fig. 48). It consists of an ingoing and an outgoing cannula which are inserted, respectively, into the proximal and distal sections of a divided artery. The blood flowing from the artery into the instrument enters a small pear-shaped flask of known capacity filled with oil. Upon the entrance of the blood the oil is forced over into another flask of identical size but which has previously

been filled with saline. The entrance of the oil forces the saline in turn into the peripheral section of the artery. When flask 1 is filled with blood and flask 2 with the transferred oil, the instrument is rotated through a semicircle. This reverses the positions of the flasks and the process of filling and emptying is repeated. The blood in flask 1 is now forced into the peripheral part of the artery as blood enters flask 2 and displaces the oil as before. From the number of fillings of the flasks during the period of observation the volume of blood flowing in a unit of time is readily calculated. This value divided by the cross area of the vessel, since velocity is inversely proportional to the sectional area, gives the lineal velocity. Thus $V =$

$\frac{v}{\pi r^2}$ where V = velocity in millimeters per second, v the volume of blood in cubic millimeters flowing into the instrument in a given time and r the radius of the artery in millimeters. For instance, if the flow is 3000 c.mm. per second and the diameter of the vessel is 4 mm., the cross area is $\pi \left(\frac{4}{2}\right)^2 = 3.14 \times 4 = 12.56$ sq.mm. and the velocity is $\frac{3000}{12.56} = 238$ mm. per second.

This determination, of course, ignores the fluctuations in velocity which occur during the cardiac cycle,¹ and in consequence gives only the average or mean velocity. It may also be recalled that the velocity is not the same at different points along the radius of the blood column, the flow being much greater in the axial part of the stream than toward the circumference.

THE *thermo-stromuhr* OF REIN. In this method the blood as it flows past a point in the vessel (which is exposed but not opened) is heated by means of electrodes connected to a high frequency current. The temperature of the blood is measured below and above the heated region by means of thermojunctions. The magnitude of the temperature difference is a function of the blood flow and is used as the basis for the calculation of the latter. The temperature difference diminishes with increased blood flow and vice versa. This method is accurate and possesses the advantage that it entails little or no disturbance of the circulation (fig. 49).

¹ The velocity rises during systole and falls during diastole. There is therefore a pulse of velocity as well as of pressure. Green and his associates found that the velocity of blood flow in the aorta of the dog rises abruptly during systole, its maximum coinciding with the peak of the pressure curve, and then declines, gradually at first and later suddenly. It reaches zero at the commencement of the protodiastolic period (p. 173). Back flow occurs during the latter period. After this, forward flow is resumed and reaches a second maximum but not as great as the first, in the middle of diastole. Velocity of flow then declines gradually to the end of diastole.

The velocity in the larger arteries of the dog during rest is from 0.1 to 0.2 meter per second, in the capillaries about 0.5 mm. per second and in the medium sized and large veins from 0.06 to 0.2 meter per second.

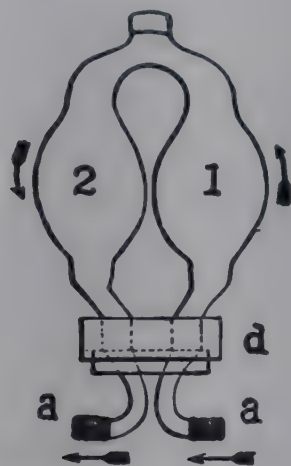


FIG. 48. Ludwig's stromuhr. 1 and 2, glass flasks; *d*, metal turn-table; *a*, *a*, section of artery. Arrows indicate direction of blood flow.

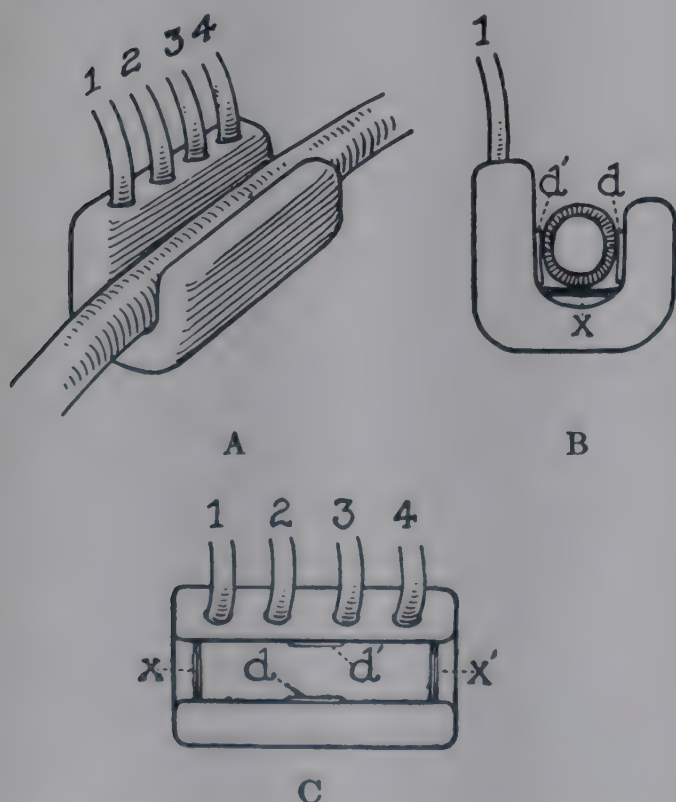


FIG. 49. Thermo-stromuhr. *A* shows its application on a blood vessel; *B* shows a cross section of the blood vessel as it lies between the electrodes (platinum plates) *d* and *d'*, and on a thermojunction *x*. *C* shows the relative positions of plates and thermojunctions. *x* and *x'* are connected to a Zeiss loop galvanometer by leads 1 and 4. *d* and *d'* are connected to leads 2 and 3 (after Herrick, Essex and Baldes).

There is no reliable method for determining the mean lineal velocity of the blood in man. Attempts are sometimes made to arrive indirectly at a rough approximation by the use of certain data obtained in other ways, e.g., output of the heart (p. 228) and the cross section of the aorta in the

cadaver (p. 117). The velocity in the latter vessel is probably around 0.4 meter per second during bodily rest. Estimations of the flow in the arteries of the arm may be made from determinations of the volume flow through the hand by the methods described below, and the diameter of the brachial.

(2) CIRCULATION TIME

By this is meant the time which a particle of blood takes to make the complete round of both the systemic and pulmonary systems—*total circulation time*—or of the pulmonary circuit alone—the *pulmonary circulation time*. That is, if the voyage of a red cell could be timed from the moment it passed a given point, say in one jugular vein, to the moment when it arrived at the point from which it started or at a corresponding point in the opposite jugular the time consumed would be the total circulation time. The red cell must have traversed in succession the jugular vein, the right heart chambers, the pulmonary vessels, the left heart chambers, the arteries and then the veins of the head and neck. The time taken in passing from the jugular to the carotid is the pulmonary circulation time.

Measurement of the circulation time. This has been accomplished in animals in various ways, e.g., by the injection of potassium ferrocyanide into the vein and having the blood from the other vein or artery fall upon a revolving drum covered with paper soaked in ferric chloride solution. The appearance of the Prussian blue reaction indicates the completion of the particular circuit which is being timed. Methylene blue may be injected and the time noted when discoloration of the opposite vessel occurs. Stewart who employed the latter method also devised an *electrical method* in which a 2 per cent solution of sodium chloride is run into the vein. Two platinum electrodes separated from one another by a short distance are laid in contact with a vessel (jugular or carotid) of the opposite side. The electrodes are connected up as a resistance in one arm of a Wheatstone bridge. This is balanced with the resistance in the other arm. As the salt solution of high electrical conductivity reaches the section of vessel beneath the electrodes the electrical balance is upset by the sudden fall in resistance which results. This is recorded by the swing of a galvanometer or the ringing of a bell.

In man the circulation times have been measured by the injection of the dye fluorescein into the arm vein of one side and timing its arrival at a corresponding vein of the opposite arm; by the intravenous injection of histamine (0.001 mgm. histamine phosphate per kilogram of body weight)

and noting the time at which the flushing of the face, due to capillary dilatation, occurs; or by injecting glucide or decholin and having the subject signal the instant that he experiences the sweet or bitter taste, respectively. In the first mentioned method the dye traverses the arm vein, the right heart chambers, the pulmonary circuit, left heart, arteries of the opposite arm, capillary bed and finally the arm vein of the opposite arm. Its arrival at a point in the latter vessel is detected by drawing off samples of blood at 5-second intervals.

Blumgart and Yens have devised a method in which an active deposit of radium is injected into the antecubital vein of one side and its arrival detected by means of an instrument sensitive to radioactivity, at the right auricle and at the antecubital *artery* of the opposite side. The detecting instrument must, of course, be shielded by means of lead sheets from the action of the radioactive substance except at these two points. The arm to arm time, less the arm to heart time, is taken as the "crude pulmonary circulation time." Since the time consumed in traversing the aorta, subclavian artery and the artery of the opposite arm is very brief (a second or less) the measurement obtained in this way must approximate very closely the true pulmonary circulation time. A more convenient method for determining the pulmonary circulation time has recently been devised by Robb and Weiss based upon the fact that cyanide stimulates the respirations through its action upon the carotid sinus; 0.11 mg. of sodium cyanide per kilogram of body weight is injected into the arm vein and the time recorded by means of a pneumograph and stop watch.

NORMAL VALUES. 1. *Total circulation time.* Between veins of the two arms (fluorescein method) average 21 seconds (12 to 26 seconds). Arm to face (histamine method), average 24 seconds.

2. *Arm vein to corresponding artery of the opposite side* (radio-active method), average 18 seconds (14 to 24 seconds).

3. *Arm to heart* (radio-active method), average 6.6 seconds (2 to 14 seconds).

4. *Pulmonary circulation time* (radio-active method), average 11 seconds (5 to 17 seconds).

The circulation time is a measure of the *shortest* time which any particle of blood takes in passing from one point in the circulation to another. It is evident that if all the blood channels between the two points are not approximately uniform in length and diameter only a part of the blood will travel from point to point at the rate indicated by the measurement. It is believed, however, that the flow of blood through the lungs occurs

at an approximately uniform rate in different vessels and that the pulmonary circulation time may be taken as an index of the mean velocity of the pulmonary blood flow. It therefore bears a relation to the total volume of blood traversing the lungs in a given time, i.e., to the output of the heart (p. 225), being short with large outputs and long when the output is small.

Knowing the pulmonary circulation time and the output of the heart per minute the volume of blood contained in the lungs may be calculated from the following equation—

$$V = Q \frac{60}{T}$$

where V = the cardiac output, Q , the quantity of blood in the lungs and T the pulmonary circulation time. Q averages about 8 per cent of the total blood volume.

A close relationship exists between the size of the animal and the circulation times, these being shorter in a small than in a large animal. This is to be expected since the distances are shorter. The pulse rate also bears a relation to the animal's size, the smaller the animal the higher the rate. As a consequence, the product of the pulse rate and the pulmonary circulation time is almost the same in different species.

The circulation times are markedly reduced (velocity of blood increased) during muscular exercise or by the injection of adrenaline. They are altered in the following pathological conditions.

A. CONDITIONS ASSOCIATED WITH A REDUCED CIRCULATION TIME:

Hyperthyroidism. The decrease is closely related to the height of the metabolic rate.

Anemia (see p. 358) the increase in blood velocity is in proportion to the reduction in oxygen-carrying capacity of the blood.

B. CONDITIONS ASSOCIATED WITH A LENGTHENED CIRCULATION TIME:

Hypertension, normal or slightly lengthened.

Myxedema.

Polycythemia vera.

Cardiac failure. The engorgement of the systemic and pulmonary vessels results in a great increase in the quantity of blood contained in the lung and peripheral vessels. The speed of the blood through these vascular areas is reduced though the total volume of blood flowing through the distended vessels in a unit of time is not necessarily diminished (see below). The improvement in cardiac action following the administration of digitalis is accompanied by shortening of the circulation time. This drug causes no effect upon blood velocity in normal persons.

Postoperative. Smith and Allen found that

starting about the 5th day after operation the foot to carotid circulation time increased gradually to the 10th day when it was 50 per cent greater than the preoperative value. These observations are pertinent to the question of postoperative thrombosis (see p. 96).

(3) THE VOLUME OF BLOOD FLOWING THROUGH AN ORGAN OR CIRCUMSCRIBED REGION OF THE BODY; THE MASS MOVEMENT OF THE BLOOD

The total volume of blood flowing through an organ in a given time should not be confused with the velocity of the blood stream in the individual vessels, i.e., the speed of the blood corpuscles which, as mentioned above, is referred to as the lineal velocity. The two do not alter to the same degree, or necessarily, indeed in the same direction. If the pressure head remains unchanged then the

If the capillaries do not alter in caliber, or do so to a minor extent when the arterioles dilate, the velocity of the blood flowing through the capillaries is also increased. If, on the other hand, the total cross area of the vascular bed of the organ is enlarged as a result of capillary dilatation an opposite effect upon the lineal velocity of the blood in these vessels is produced which tends to counteract the effect upon velocity caused by the arteriolar dilatation (velocity being inversely proportional to the cross area of the vascular bed, p. 114). It thus comes about that with a constant arterial pressure the speed of the blood in the capillaries of a part may be reduced though the total volume of blood passing through it remains unaltered or is even increased. In the case of the lungs, for example, whose vessels of course offer the only route for the blood from the right to the left side of the heart,

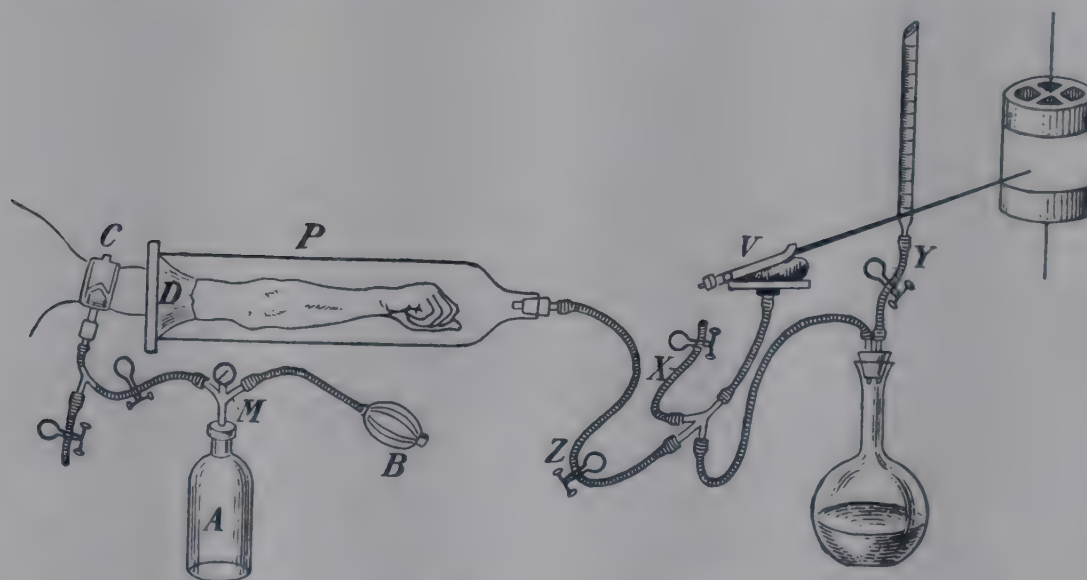


FIG. 50. Diagram showing Hewlett and Van Zwaluwenburg's method for estimating the rate of blood flow in the arm (after Hewlett and Van Zwaluwenburg).

volume of liquid flowing in a unit of time along a narrow tube comparable in size to the small and medium sized arteries is proportional to the fourth power of the diameter of the tube. The lineal velocity, on the other hand, is proportional only to the sectional area of the tube (p. 114). When the arterioles of an organ dilate, though the peripheral resistance is reduced locally, compensatory vasoconstriction in other vascular areas occurs (Lovén reflex, p. 246) and a fall in general blood pressure does not ordinarily result. That is, the pressure head in the vessels feeding the organ remains at, or may even rise above, its original level. A greater volume of blood therefore flows through the organ and the velocity of the blood in its larger vessels increases. The capillary blood pressure increases for, as a result of dilatation of the arterioles, less energy is expended in overcoming the frictional resistance in these vessels

dilatation or constriction of the arterioles and capillaries unaccompanied by any change in the output of the right ventricle will not alter the volume of the pulmonary blood flow. The velocity of the blood through the small vessels will, however, be reduced or increased respectively with the expansion or constriction of the pulmonary vascular bed. Conversely, owing to the occurrence of compensatory changes in the capacity of the vascular bed, a reduction or increase in the cardiac output (and so of the quantity of blood passing through the lungs or through the peripheral parts of the body) does not necessarily alter the velocity of the blood through the individual vessels of the pulmonary or systemic circuits.

Approximate values for the volume flow per 100 grams of tissue per minute for various organs of animals are given below:

Thyroid.....	560 cc.	
Kidney.....	150 cc.	
Liver.....	150 cc.	{ arterial, 35 cc. portal, 115 cc.
Brain.....	136 cc.	
Intestines.....	70 cc.	
Spleen.....	40 cc.	
Stomach.....	25 cc.	

In *animals* one of three methods may be employed for the measurement of the volume flow through an organ.

(1) The simplest method is to collect and measure the blood issuing from the vein or veins of the part. This method can be employed only over relatively short periods and with small well circumscribed organs such as the kidney or salivary gland.

(2) If there is a single artery or vein supplying or draining the organ the stromuhr may be inserted into either vessel and the quantity of blood measured which enters or leaves the region, or the thermostromuhr method may be employed (p. 145).

(3) *The plethysmographic method of Brodie.* This is based upon the principle that if the venous return be occluded any change in volume of the part which results during the period of occlusion must represent the amount of blood which has entered the part during that period. The time during which the vein is compressed and consequently the duration of the observation must obviously be brief, for interference with the venous flow will automatically slow the blood stream and give a fallacious result. The organ, e.g., the kidney, with its blood vessels intact, is placed in an air-tight chamber (plethysmograph, p. 251). At the point where the vessels enter and leave the chamber a non-resistant material, e.g., sponge or tow packing smeared with vaseline, is used to form a hermetic seal so that compression of the vessels is prevented. A tube leads from the interior of the chamber to a tambour and recording apparatus. The excursions of the latter are calibrated to represent cubic centimeters of blood. To estimate the blood flow the vein is suddenly clamped and the increase in volume of the organ recorded over a short period. The method has been claimed by Brodie to give results comparable in accuracy with those obtained by means of the stromuhr. Brodie's method

has been adapted by Hewlett and Van Zwaluwenburg to the estimation of the volume flow in the human hand and forearm. A narrow cuff encircling the upper arm is employed to compress the veins (fig. 50).

The calorimetric method. This was devised by G. N. Stewart for the measurement of the volume flow through the human hand. Briefly, the method is based upon two assumptions (1) that the hand is a perfect radiator, and when immersed in a small body of water the blood coursing through its vessels gives up heat, so that its temperature comes to equal the average temperature of the surrounding water during the course of the observation,² (2) that the blood is the only source of heat, the heat generated by the muscular tissue of the hand being negligible.

The amount of heat (gram calories) given out by the hand to the water is obtained by multiplying the quantity of water in grams by the number of degrees centigrade through which its temperature has been raised. The blood flow in grams during the whole period of the observations is obtained from the following formula—

$$Q = \frac{H}{T - T^1} \times \frac{1}{S}$$

where Q equals the quantity of blood (grams), H the heat (gram calories) given out to the water, T and T¹ the temperatures of the arterial and venous bloods respectively and S the specific heat of blood (0.8). The difference between T and T¹ represents the drop in temperature of blood in passing from the arterial to the venous side.

A pair of specially designed water calorimeters of about 3000 cc. capacity are employed for the observations.

The blood flow through the hand is thought to be indicative in a general way of the flow through the peripheral parts of the body. The normal flow at ordinary room temperature 65°F. has an average of about 13 grams per minute per 100 grams of hand substance. A rise in the environmental temperature causes a marked rise, a fall in temperature curtails the flow.

² That the temperature of the venous blood may be taken as that of the average temperature of the water in the calorimeter has been questioned by Sheard.

CHAPTER XVIII

THE ARTERIAL PULSE

THE NATURE OF THE PULSE WAVE

The pulse is the pressure change created by the ejection of blood from the heart into the already full aorta and propagated as a wave through the blood column and arterial wall to the periphery. If the walls of the system were absolutely rigid, since liquids are incompressible, an impact delivered at one end would cause a pressure change to be transmitted instantaneously as through a steel rod to the furthestmost parts. In the case of elastic tubing, such as composes the vascular system, the pressure change is accompanied by an expansion of the tube's wall. It should be emphasized that the extra blood which is thrown into the aorta and the pulse wave which is the direct result of the former, do not pass along the vessel in company. If the ejected blood were made distinguishable in some way and its speed compared with that of the pulse wave it would be found that the latter travelled at a rate from 10 to 15 times faster than the former. The speed of the blood depends upon factors which have been considered elsewhere, e.g., pressure gradient, cross-sectional area of the vascular bed, etc., while the velocity of the pulse wave is determined almost entirely by the resilience of the arterial wall.

The independence of the velocity of a liquid and of a wave in that liquid will be evident if one considers what occurs when, say, a bucket of water is thrown into a running stream. Waves are then set up which travel through the water at a rate which has no relation to the velocity of the stream itself. They run up the stream against the current as well as down. Though the pulse wave in its passage gives some forward movement to the blood, i.e., increases its velocity at the moment of its passage just as a wave upon a river slightly speeds the flow of water, as is shown by the impetus which it gives to a floating cork, yet the chief phenomenon is a propagation of a change of form and pressure. It is a molecular movement rather than a translation of fluid en masse. The particles of the fluid change their positions relative to one another, but to a comparatively small extent in relation to the arterial wall—a pulse wave travels through a perfectly stagnant blood column, as in a ligated vessel. This distinction may be illustrated by the diagram in figure 51.

Measurement of the speed and length of the pulse wave

The velocity of the pulse wave in the brachial artery is normally from 5 to 8 meters per second. By means

of a pair of tambours, writing levers and a time marker (p. 189) the difference in the times of arrival of the pulse wave at a near and at a far point of the vascular system can be determined. The time difference divided into the distance travelled between the two points gives the velocity of propagation of the wave. Thus—

$$\frac{\text{Distance in mm.}}{\text{Time in seconds}} = \text{velocity in mm. per second}$$

Since the rate of propagation of the pulse alters with the state of the arterial wall, increased rigidity causing more rapid transmission and vice versa, the velocity is increased in old age or when the elasticity of the vessels is reduced by disease, e.g., arteriosclerosis. Bramwell, Hill and McSwiney found a speed of 5.2 meters per second at the age of 5, and one of 8.6 meters per second at 84 years. Also in hypertension (pathological or resulting from muscular exercise) the walls of the vessels are more strongly stretched and thus are nearer their elastic limit; the pulse wave is therefore transmitted at a higher speed. Vaso-dilatation or low pressure from any cause, on the other hand, reduces the velocity of the pulse wave. The femoral artery is less distensible than the brachial and the velocity of the pulse is greater in the former vessel.

The length of the pulse wave. The length of a pulse wave tracing gives no indication of the length of the pulse wave itself. The tracing is inscribed by the rise and fall of the lever as the wave passes the point in the artery (fig. 52) and its length depends upon the rate at which the writing surface moves. When the rate is fast the curve is lengthened and vice versa. The pulse wave itself is in reality a very long swell or billow. The ejection of blood from the ventricle does not cause simply a small local dilatation but an extensive expansion of the arterial channels.¹ The wave measures from 3.50 to 5 meters and consequently the greater part has disappeared from the periphery before its end has left the aorta. The length of the wave may be determined from the following formula. $L = VT$, where L equals length of wave, V the velocity of transmission and T

¹ It is also to be remembered that the amplitude of the pulse wave is no criterion of the actual height of the blood pressure, for it may be low with a high blood pressure or *vice versa*. The pulse tracing or *sphygmogram* (p. 151) can give no absolute or quantitative information regarding any phase of the arterial blood pressure. It is merely a record of the movements of the vessel walls brought about by pressure variations. The movements of the wall of a peripheral artery are very slight, but in the sphygmograph tracing they are magnified several times. When the pulse is felt by the finger placed upon the radial artery it is the pressure change—the impact of the pulse wave—rather than the actual movement of the vessel wall which is detected.

the time the wave takes to pass any point. The manner of obtaining V has been described above. T may be obtained from the time markings on the pulse tracing or simply from the pulse rate. If, for example, 70 pulses pass a point in the artery per minute, each must require $\frac{6}{7}$ second for its passage.

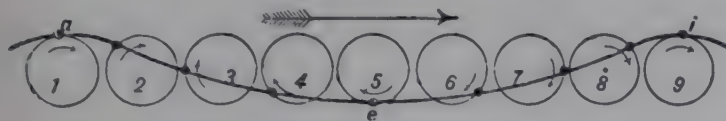


FIG. 51. Motion in a water wave. Nine equidistant water particles are represented by dots. The particles move in vertical circles with fixed centers, all with the same uniform velocity. The position of each particle in its orbit is called the *phase* of its motion. In the diagram each particle differs in phase from the next by one-eighth of a full revolution. At the top of the circle each particle moves in the direction of travel of the wave (as indicated by the large arrow); those towards the bottom move in the opposite direction. The particles upon the crests of the wave, a and i , are the same phase and in a phase opposite to that of e , in the trough of the wave. After the wave has passed the particles come to rest and may show no change from their original positions. The length of the wave is the distance between two particles in the same phase. (Modified from Kimball's *Textbook of Physics*.)

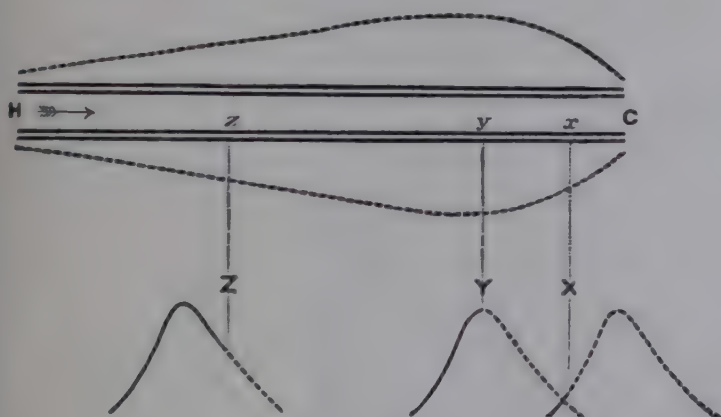


FIG. 52. Diagram representing a pulse wave passing over an artery. Heavy double line, artery at rest; dotted line, artery expanded. Curves X, Y and Z are drawn during the passage of the wave (in the direction indicated by the arrow) by three levers placed upon the vessel at x , y , z . At Z the greater part of the wave has passed beneath the lever at z , as shown by the continuous line of the first curve, and has still to describe the smaller part represented by the broken line. In Y the lever at y is at the summit of the wave. At X the lever x has just commenced to rise and the greater part of the curve has still to be inscribed as indicated by the dotted line (after Foster).

Analysis of the pulse curve

The pulse wave may be made to describe a curve by laying a light lever upon an artery, e.g., the radial, and having it record its excursion upon a moving surface as the artery expands and recoils beneath it. The means of doing this is provided by an instrument known as a *sphygmograph*. One of the best known of these is Dudgeon's shown in figure 53. The curve consists of an abrupt almost vertical upstroke, the *anacrotic limb*, and a more

gradually sloping downstroke, the *catacrotic limb*. The rising limb is inscribed first and represents the front of the pulse wave, while the catacrotic limb is drawn during the fall of the lever, i.e., after the crest of the wave has passed. Though under abnormal conditions of the circulation (see below)

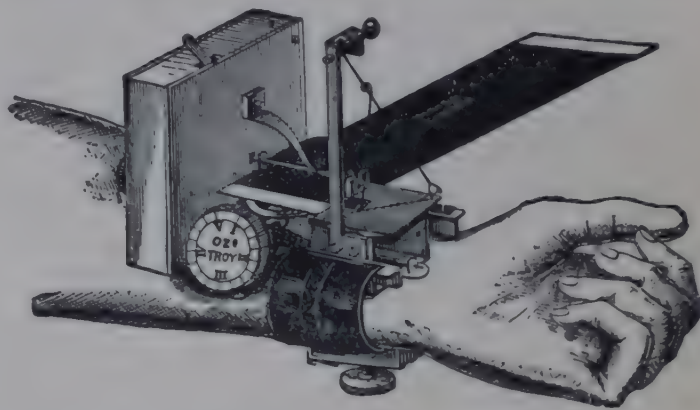


FIG. 53. Dudgeon's sphygmograph, applied to the radial artery.

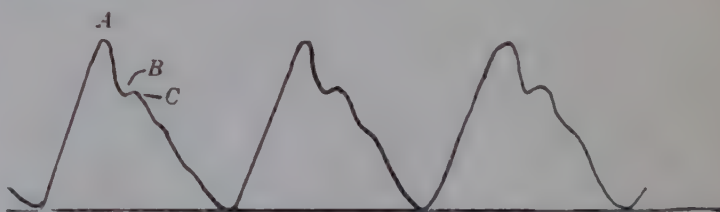


FIG. 54. The pulse wave. A. Primary wave, B. Dicrotic notch, C. Dicrotic wave.

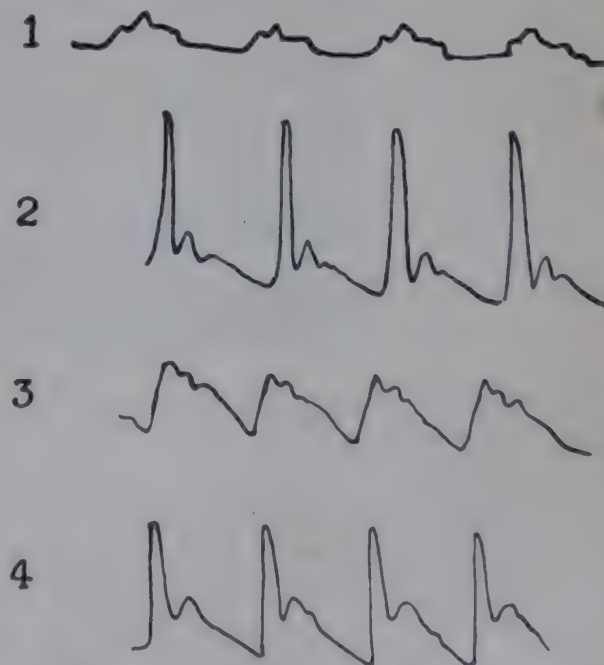


FIG. 55. Abnormal pulse curves. 1, aortic stenosis, 2, aortic regurgitation, 3, arterial hypertension, 4, arterial hypotension.

the anacrotic limb may show one or more secondary waves, it is under ordinary circumstances smooth and uninterrupted. The descending limb, on the other hand, shows a well-marked negative wave, i.e., a depression, followed by a positive wave. These are known as the *dicrotic notch* and *dicrotic wave*, respectively. Under certain conditions the

dicrotic wave may be so well-marked that it can be felt as a separate impulse by the finger placed upon the radial artery. Often less well-marked wavelets preceding the dicrotic notch (*predicrotic waves*) are present. Other waves (*postdicrotic*) may follow the dicrotic wave (fig. 54).

The dicrotic wave and notch are produced in the following way. As ventricular systole comes to an end and the intra-ventricular pressure falls below the aortic, pressure eddies bring the aortic valves into apposition; at the same time the distended elastic arterial wall rebounds and pressing upon the blood forces it centrally as well as thrusting it forward toward the periphery. The swing of the blood column toward the heart sets up a

charge, (b) the output per beat, (c) the height of the diastolic pressure and (d) distensibility of the arterial walls. With a slow rate of ejection such as occurs in narrowing of the aortic ring (stenosis) the upstroke is gradual, the wave usually of low amplitude and a secondary fluctuation may appear (anacrotic wave) which in some instances is actually higher than the primary wave (fig. 55, 1). Secondary waves upon the anacrotic limb are also found in aortic aneurysm or when the aorta is narrowed as a result of a developmental defect or by pressure from without. These waves on the anacrotic limb are probably reflected from the periphery of the circulation, the long period of ejection permitting waves to travel centrally and meet the primary wave before it has reached its crest. When the discharge is rapid, the output large, or the

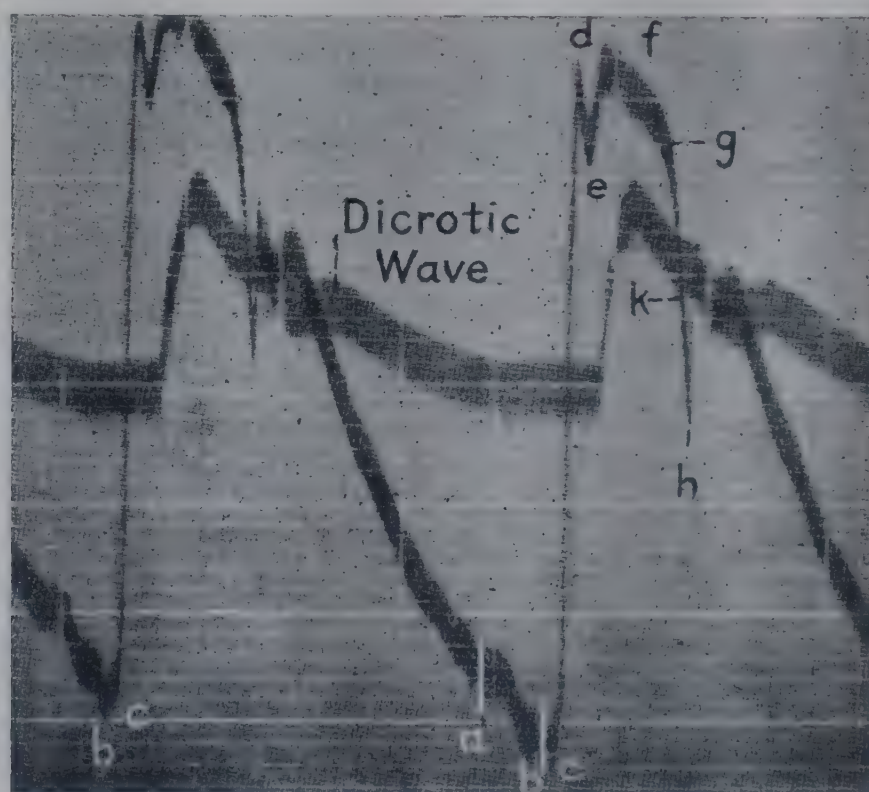


FIG. 56. Tracing showing the difference between the subclavian (central) and radial (peripheral) pulse in man. The delay of the radial pulse is clearly shown (after Wiggers).

negative fluctuation which is propagated in the wake of the main or primary wave throughout the arterial tree and is represented by the dicrotic notch on the pulse tracing. The next instant the aortic valves which have been forced toward the ventricular cavity become taut, the movement of the blood column is abruptly checked and rebounds from their surfaces. This sets up a positive pressure change which appears in the pulse tracing as the dicrotic wave.

Variations in the form of the pulse curve

The slope of the *ascending limb* is dependent upon several factors, (a) the duration of the ventricular dis-

charge, (b) the output per beat, (c) the height of the diastolic pressure and (d) distensibility of the arterial walls. With a slow rate of ejection such as occurs in narrowing of the aortic ring (stenosis) the upstroke is gradual, the wave usually of low amplitude and a secondary fluctuation may appear (anacrotic wave) which in some instances is actually higher than the primary wave (fig. 55, 1). Secondary waves upon the anacrotic limb are also found in aortic aneurysm or when the aorta is narrowed as a result of a developmental defect or by pressure from without. These waves on the anacrotic limb are probably reflected from the periphery of the circulation, the long period of ejection permitting waves to travel centrally and meet the primary wave before it has reached its crest. When the discharge is rapid, the output large, or the

diastolic pressure low, the pulse wave tends to be of large amplitude and its upstroke steep (fig. 55, 4). The slope of the *descending limb* is abrupt when the diastolic pressure is low as in aortic regurgitation or arterio-venous aneurysm (fig. 55, 2). Any state which renders the arterial walls less tense will tend to increase the magnitude of the dicrotic fluctuations and to produce other secondary waves (predicrotic and postdicrotic) which under ordinary circumstances do not appear. If, for example, the arterial system is underfilled, as a result of haemorrhage or vasodilatation, or a low diastolic pressure from whatever cause exists, the dicrotic wave becomes prominent; under such conditions as in typhoid fever, it may sometimes be felt with the finger as a distinct tap following the primary wave. The pulse is then said to be dicrotic.

THE PULSE WAVE IN DIFFERENT REGIONS.

CENTRAL ARTERIAL PULSE

Pulse tracings recorded at different parts of the arterial tree show that the conformation of the wave changes as it travels toward the periphery. The rise and fall of the primary wave are more gradual and the amplitude is less in the smaller arteries. A pulse curve taken from a central artery such as the subclavian differs very strikingly from the typical tracing taken from a peripheral artery such as the radial. Instead of the usual comparatively shallow dicrotic notch and rounded wave, a sharp depression (*incisura*) followed by a sharp spike is seen in the subclavian tracing. Such a record may be obtained from the human subclavian by means of a small conical cup pressed into the supraclavicular fossa and connected with an optical recording apparatus (fig. 56). A *central arterial pulse* shows two preliminary vibrations. These immediately precede the main upstroke, i.e., they occur before the opening of the semilunar valves, and result from pres-

sure changes transmitted through these delicate structures. The first (a-b) is due to auricular systole; the second (b-c) to the tension developed at the beginning of ventricular systole (isometric period, p. 172). The ejection of blood from the ventricle causes a sharp rise in pressure which, setting the blood column into vibration causes the fluctuations c, d, e. The pressure mounts to f and is sustained for a time, but then as systole comes to an end it drops precipitately to produce a deep depression—the *incisura* (g-h). This occurs during the closure of the semilunar valves and corresponds to the so-called protodiastolic period of ventricular diastole (p. 173). Several waves follow the *incisura*, due to after-vibrations of the valves. In their transmission through the arterial wall to peripheral points minor fluctuations of the central pulse become fused to produce smooth contours, while the primary oscillations, the *incisura*, and the after vibrations become dampened down and appear eventually as the primary wave and dicrotic fluctuations of the distal arterial tracings.

CHAPTER XIX

THE PHYSIOLOGY OF CARDIAC MUSCLE. PERFUSION OF THE ISOLATED HEART

HISTOLOGY OF CARDIAC MUSCLE

Cardiac muscle fibers, like those of voluntary muscle, have transverse as well as longitudinal striations. But the investing sarcolemmal sheaths of the cardiac fibers, unlike those of skeletal muscle are ill-defined and the muscle cells communicate with one another through branches or bridges of protoplasm (fig. 57). So, the cardiac muscle, rather than being a collection of separate fibers, has the characters of a syncytium—a continuous multinucleated sheet over which an impulse may spread without interruption in any direction. The cross striations are less distinct than in skeletal muscle, the sarcoplasm is more abundant and the nuclei are embedded in the center of the cell.

THE PHYSIOLOGICAL PROPERTIES OF HEART MUSCLE

These may be considered under the following heads: (1) *Excitability and contractility*, (2) *rhythmicity*, and (3) *conductivity*.

(1) *Excitability and contractility*

The ability of a tissue to respond to a stimulus is spoken of as excitability or irritability. In the case of muscle the response is a shortening of its fibers. Certain features of the contraction of cardiac muscle will now be discussed.

(a) THE "ALL OR NONE" LAW. This states that the weakest stimulus that is capable of causing a contraction at all (minimal stimulus) will produce the maximal contraction. This fundamental fact, which was first demonstrated by Bowditch in 1871 in cardiac muscle, has since been found to be true also for nerve and skeletal muscle. Though a skeletal muscle responds to stimuli of graded strengths by contractions of graded amplitude and so apparently differs from cardiac muscle, it can be shown that a single skeletal fiber obeys the "all or none" law. The apparent difference in behavior between cardiac and skeletal muscle is due to the fact that the former is a continuous protoplasmic sheet, and an impulse which causes contraction in one part spreads under ordinary circumstances and involves the whole. The individual fibers in skeletal muscle, on the other hand, are insulated from one another. The graded response of the *entire* skeletal muscle means simply that more

fibers are excited by the stronger than by the weaker stimulus.

It must be pointed out that a minimal stimulus at one time may at another be subminimal should the excitability of the muscle be reduced. On the other hand, should the excitability be increased an ineffective stimulus may be rendered effective. Consequently, when it is said that the cardiac muscle follows the "all or none" law it is to be remembered that this applies only to the conditions existing at the time. The excitability and contractility of the muscle is variable and a stimulus which under one set of conditions would produce a weak contraction would under more favorable conditions produce a much greater response. Length of the fiber, hydrogen ion concentration, state of nutrition, fatigue and the inorganic constitution of the fluid bathing the heart (p. 157) are among the factors which influence its excitability and the force of its cardiac contraction.

(b) TREPPE. This phenomenon was also first observed by Bowditch in cardiac muscle, though it is also shown by skeletal muscle. If a number of stimuli of the same intensity (maximal) be sent into the muscle after a resting period, the first few contractions of the series show a successive increase in amplitude. This ascent in the magnitude of the responses at the beginning of the series suggests the rising steps of a stair case (German *treppe*) and is supposed to be due to the greater contractility of the muscle at this time, resulting from the rise in temperature and the slight increase in H ion concentration of the muscle as a result of lactic acid production. This apparent contradiction of the "all or none" law is explained by the considerations in the foregoing paragraph.

(c) THE REFRACTORY PERIOD. The refractory period of skeletal muscle is very brief (0.01 second) and corresponds to the latent period, i.e., the period elapsing between the receipt of the stimulus and the commencement of the contraction. A stimulus applied to the muscle any time after it has commenced to contract causes a second contraction which is added to the first (*summation*). A rapid series of stimuli timed to fall in each instance just after the refractory period of the preceding contraction will produce a rapid series of

shortenings of the muscle which fuse into an apparently maximal contraction (*tetanus*). The contraction is sustained as long as the stimulation is continued or until fatigue sets in. Heart muscle behaves differently. Its refractory period is relatively long and lasts throughout the contraction phase. *The muscle will not respond to a second stimulus, no matter how strong, so long as its fibers are still in the contracted state.*¹ This is the *absolute refractory period*.

The time interval following a previous excitation during which stimulus will not elicit an impulse of sufficient intensity to be conducted through the cardiac muscle is termed by Drury the "*effective refractory period*."

During relaxation the muscle regains its excitability gradually. Early in the relaxation phase



FIG. 57. Cardiac muscle fibers

the strength of stimulus required to produce a response is greater and the response to a given stimulus is less than later on. Not until complete relaxation has occurred does the excitability of the muscle return to its normal value. This period of time during which excitability is depressed but not abolished is called the *relative refractory period*. The latent period of the response, that is, the time elapsing from the application of the stimulus to the contraction of the ventricle, is the same whether the latter is induced early or late in the relative refractory period (Woodsworth, Fiddes). The lengthening of the latent period found by Marey and illustrated in his tracing (fig. 58) was apparently due to inadvertent stimulation of the auricle

¹ Wiggers finds that the refractory period of the heart does not last for the entire duration of its contraction but that it responds by a contraction early in diastole to a stimulus applied within the last 0.06 seconds of systole.

by the leakage of current from the electrodes applied to the ventricle. The variability of the latent period in these classical experiments is therefore considered to be of supraventricular origin.

It will be noted from a reference to figure 57⁵⁸ that a long pause follows the contraction caused by the artificial stimulus. The artificially induced contraction is called an *extra systole* or *premature contraction*. The long interval following the *extra-systole* is termed the *compensatory pause*

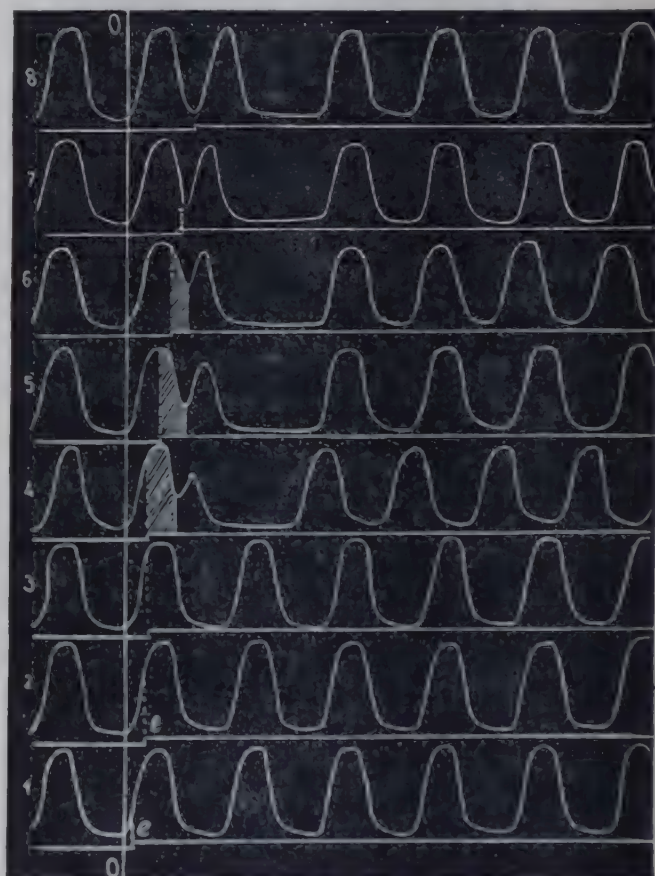


FIG. 58. Myograms of frog's ventricle, showing effect of excitation by break induction shocks at various moments of the cardiac cycle. The line 0, 0 indicates in all tracings the commencement of the beats during which the shocks were sent in. It will be noted that in 1, 2 and 3 the heart is refractory to the stimulus. The signal (the break in the horizontal line) indicates the moment at which the stimulus was applied. The latent period (hatched area) does not alter as this figure shows. See text. The extrasystoles increase in height from 4 to 8, each being followed by a compensatory pause (after Marey).

since its duration is such that when the next normal beat is resumed it occurs at precisely the same time, i.e., at the same point in the tracing, as it would have appeared had no premature contraction been provoked. The occurrence of the long pause is explained as follows. The normal impulses pass from the auricle to the ventricle in a perpetual stream and in orderly sequence. When the ventricular muscle is stimulated artificially during diastole, and an extra contraction induced, the normal impulse when it arrives from the

auricle at the usual time finds the ventricle already in the contracted state and, in consequence, refractory. The impulse is therefore ineffective. Not until the arrival of the next normal impulse is the muscle in a condition to respond.² This accounts for the fact that the time elapsing between the normal beats preceding and following, respectively, the premature contraction is equal to the length of two normal cardiac cycles. In other words, the heart after the interruption in its rhythm again "gets into step."

The long refractory periods of the cardiac muscle serve to preserve the cardiac rhythm. The absolute refractory phase makes the summation of contractions and the production of tetanus impossible. The relative refractory period tends to discourage the occurrence of a second contraction before sufficient time has elapsed to allow the complete relaxation of the muscle from a preceding contraction. When a premature contraction does occur its refractory period serves to restore the normal rhythm.

The absolute refractory period may be altered by various agencies. It is shortened by rise in temperature and rapid heart action (see p. 200). It is prolonged by the action of certain drugs (p. 202). Vagal stimulation shortens the refractory period of the auricular muscle but has no effect upon that of the ventricular muscle (p. 202).

(2) *Rhythmicity and (3) conductivity*

These properties of cardiac muscle will be considered in subsequent pages.

Cardiac tonus

The subject of tonus in mammalian cardiac muscle has been beset with conflicting opinions.

² Sometimes when the premature contraction occurs early in diastole, being very weak and short it is over before the next normal impulse arrives. Therefore a long pause does not appear. An extra contraction situated between two normal beats and not followed by a long pause is called an *interpolated extra-systole*. The underlying processes responsible for the refractory periods, absolute and relative, are unknown. They have, however, been given a somewhat picturesque explanation based upon the assumption that the cardiac contraction results from the liberation of energy accumulated during the diastolic period. During systole this energy is "touched off" by the cardiac impulse and discharged. At the end of the contraction phase it has been completely dissipated, a second stimulus is therefore ineffective. In early diastole a relatively small amount of energy has accumulated and a stimulus applied at this time in consequence calls forth a very weak response. Subsequent responses correspond to the amount of energy built up, between the previous systole and the application of the stimulus. This conception is useful for purposes of illustration but it gives little aid in gaining an insight into the fundamental processes concerned.

Rhythmical tonus changes were demonstrated by Fano in the auricle of the tortoise. This observation has been repeatedly confirmed, yet it should not be cited in support of the view that tonus is a property of the mammalian heart since the rhythmic changes were shown by Bottazzi to arise in a sheet of smooth muscle lying beneath the endocardium and not in the cardiac fibers proper. Tissue of this nature is absent from the warm-blooded heart and from the ventricle of cold-blooded animals. Tone in the ventricles of the latter as well as in either chamber of the mammalian heart has yet to be demonstrated.

A great deal of confusion has arisen regarding the question of cardiac tone, through different interpretations having been given to the term itself. Tonus of muscle in the usual physiological sense means that state of partial and sustained contraction by which the muscle offers resistance to being stretched above or in addition to that which is offered by its purely physical properties. For instance, a skeletal muscle at rest and in connection with the central nervous system exhibits a slight but definite and persistent contraction. Less force is required to lengthen it when the nerves are cut and the tonic contraction disappears. The resistance which the muscle offers after this is dependent purely upon its inherent physical qualities, such as may be possessed by non-viable material, e.g., an elastic band.

With regard to the muscle of the heart the question is this. During diastole, does a certain degree of slight contraction—tonus—persist which offers some resistance to the inflowing blood and in consequence influences at this time the length to which the fiber is stretched? There is little definite evidence that tonus in this sense is possessed by the mammalian heart muscle; but variations in extensibility of cardiac muscle are admittedly more difficult of investigation than are those of skeletal muscle. In the intact heart the only means available for such a determination is the detection of a change in the volume of the heart when a single experimental condition which might be expected to affect tonus is altered while all other factors are kept at constant values. The capacity of the ventricular cavity can increase only, of course, by a lengthening of the cardiac fibers, therefore the volume of the ventricle during diastole (diastolic volume) will give during this period an index of fiber length. Variations in the latter can be taken to represent tonus changes only when other influences which will affect the diastolic volume are eliminated. For instance, increase or decrease in the venous return during the experiment would alter the fiber length; variations in the duration of diastole would also influence the diastolic volume, since more blood will flow into the ventricle during a long than during a short diastolic period. These factors must therefore be adequately controlled before justifiable conclusions concerning tonus changes can be drawn. Apparently the constancy of the experimental condi-

tions has not always been assured and erroneous judgments upon cardiac tonus have been pronounced.

Evidence of tonus changes derived from the action of drugs upon the heart are inadmissible since abnormal conditions may be thereby induced.

It has been customary to use the term "tone" somewhat loosely, and to refer to a heart showing a large or small diastolic volume as possessing "low tone" or "high tone" respectively. But as just stated the difference in volume may be the result of other factors and need have nothing to do with tone.

PERFUSION OF THE ISOLATED HEART; NUTRITION AND OXYGEN REQUIREMENT OF THE CARDIAC MUSCLE

The frog's heart possesses no circulatory system, but merely obtains its oxygen and the necessary nutrient materials from the fluid which bathes it. In order to perfuse successfully the excised heart of higher animals certain special conditions must be fulfilled. When this has been done the mammalian heart (not excepting the heart of the human subject excised shortly after death) may continue to beat for several hours.³

The following requirements must be satisfied in carrying out the perfusion of the mammalian heart.

(1) Pressure

It is essential that the perfusion fluid be delivered under sufficient pressure in order to drive it through the coronary circulation. This is accomplished by means of a reservoir raised to a height equivalent to the normal aortic blood pressure (i.e., about 5 feet). Following the method of Langendorff a cannula is tied into the aorta. The heart is allowed to hang from the cannula which is fixed to a support and connected by tubing to the supplying reservoir. The aortic valves are brought naturally into apposition by the pressure of the fluid, which then enters the coronary arteries. Little or no fluid enters the left ventricle from the aorta; after completing the coronary circuit it escapes into the right auricle by the coronary sinus. A smaller amount enters the ventricles through the veins of Thebesius and other channels (p. 274).

(2) Temperature

The perfusion fluid is maintained at body temperature by passing it through a glass or metal worm immersed in a water bath whose temperature

³ Mann and his colleagues have succeeded in transplanting the heart from one dog to another and having it beat regularly for eight days.

may be regulated by a thermostat. Increase or decrease in temperature causes a corresponding change in heart rate. The rate of the frog's heart is doubled by a 10°C. rise in temperature between 4° and 20°C. That is, the temperature coefficient is about 2 (fig. 59). A corresponding relationship between heart rate and temperature holds for the mammalian heart within the temperature range from 26° and 40°C.

(3) Oxygen supply

This is furnished by bubbling oxygen or compressed air through the perfusion fluid. The oxygen consumption of the heart in a heart-lung preparation under conditions approximately those of bodily rest was found by Evans and Starling to

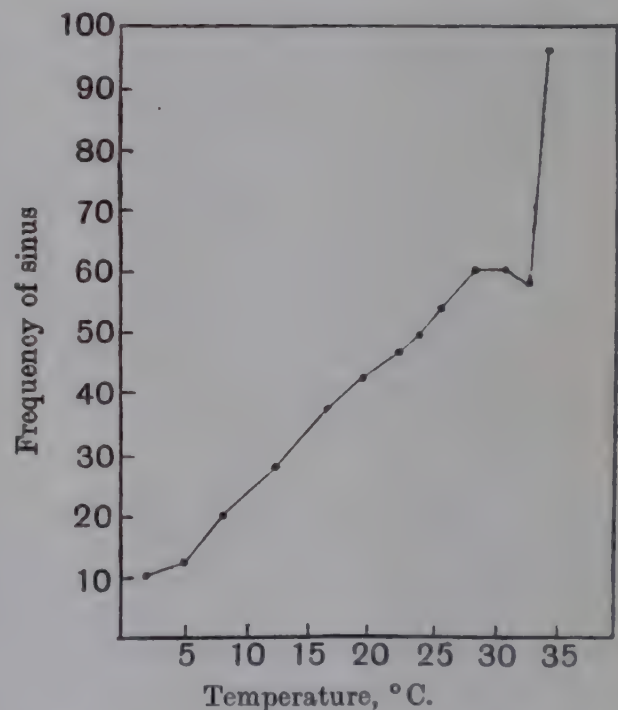


FIG. 59. Showing the linear relation of temperature to heart rate over a range of about 30°C. in South African frog (Taylor).

average 3.24 cc. per gram of heart tissue per hour. The oxygen consumption of the isolated heart is probably much less than this. During maximum work, on the other hand, the heart of the intact animal probably consumes oxygen at the rate of 40 cc. or more per gram per hour. Experiments with the heart-lung preparation show that the oxygen usage is directly proportional to the work performed by the heart, which in turn runs parallel with the length of the muscle fiber (p. 217). The oxygen consumption of the heart is greatly increased by the addition of adrenaline to the perfusion fluid. The efficiency of the heart is also increased by adrenaline in physiological dosage.

Cardiac muscle is capable of contracting only a small oxygen debt (p. 618) and ceases to function

normally when the latter amounts to 0.06 cc. per gram of tissue, that is, about a fifth of the debt which skeletal muscle can contract (0.30 cc. per gram). The heart muscle is highly sensitive to changes in pH and has a much lower buffering power than has skeletal muscle. As a consequence, when the lactic acid reaches a concentration of about 0.07 per cent in heart muscle extra-systoles, heart block or other irregularities occur, followed by cessation of the beat. Skeletal muscle, on the other hand, continues to contract until a lactic acid concentration of over 0.2 per cent is reached. The mammalian heart is unable to do work for more than 5 or 10 minutes after its oxygen supply has been cut off.

(4) Chemical constituents

Blood serum or defibrinated blood, or whole blood to which hirudin or heparin has been added may be employed as the perfusion fluid. An artificial fluid, however, is frequently used but it must imitate the plasma in so far as the chief inorganic salts of the latter are concerned.

Such a solution is that first devised by Ringer, who drew attention to the importance of the three cations, Na⁺, K⁺ and Ca⁺⁺ in the same proportions as they exist in plasma, for the maintenance of the normal action of the heart.

Ringer's solution contains the three elements in the form of the chlorides of sodium, potassium and calcium. Several modifications of this original fluid have been made. *Locke's* solution, for instance, contains in addition *sodium bicarbonate* and *glucose*. *Tyrode's* solution is similar to the former but also contains a small percentage of *magnesium chloride* and of the *acid* and *sodium phosphates*. The phosphates are designed to give the solution an optimum concentration in H ions. Table 15 gives the percentage compositions of the three different fluids. The nitrogenous constituents of blood serum, e.g., proteins, urea, etc. apparently have little effect upon the beat.

Clarke found, however, that a frog's heart after perfusion for some hours passed into a "hypodynamic" state. Contraction and conduction became greatly impaired. This condition was attributed to the removal of lipid materials from the muscle cells. The addition of certain lipid materials partially restored the heart to its previous condition.

The actions of the different cations upon the heart beat

Ringer observed that if the heart were perfused with 0.6 per cent sodium chloride solution a few beats were executed, but the heart then stopped in diastole. The addition of calcium restored the

beat for a time but the heart again came to a standstill, this time in systole. The addition of potassium antagonized the calcium effect; the beat recommenced and was maintained.

It is now well known that calcium in excess, or in normal concentration, but in the absence of potassium, lengthen systole at the expense of diastole. The heart finally stops in the fully contracted state—*calcium rigor*. Potassium acts in a reverse manner if in excess or unbalanced by calcium. More and more of the cardiac cycle is occupied by diastole and the heart ultimately comes to rest in the completely relaxed state—*potassium inhibition*. A solution containing calcium and potassium alone will not sustain the beat; sodium is essential. The manner in which sodium acts is not so clearly demonstrable as in the case of the other cations, but it is certain that the

TABLE 15
Percentage composition of perfusion fluids

	RINGER'S (MODIFIED FOR MAMMALIAN HEART)	LOCKE'S	TYRODE'S
NaCl.....	0.900	0.900	0.900
KCl.....	0.030	0.024	0.02
CaCl ₂	0.025	0.042	0.02
MgCl ₂			0.01
Glucose.....		0.1	0.1
NaHCO ₃	0.020	0.020	0.1
NaH ₂ PO ₄			0.005

excitability and contractility of the heart muscle cannot be maintained in its absence.

It is apparent than that these three cations are absolutely necessary for the normal beat of the heart, the calcium increasing the contractility and prolonging systole. Potassium has the reverse effect, reducing contractility and favoring relaxation. The presence of these substances in proper proportion ensures the rhythmicity of the contractions. It would appear, however, that potassium is of less importance than the other two, since the turtle's heart will beat for a time when this ion is absent. On the other hand, this may simply be due to the well known fact that the muscle cells have themselves a rich store of potassium. With regard to other bivalent cations, strontium, though less efficient, can replace calcium in the perfusion fluid, but barium is toxic, and magnesium is inert.

Of the underlying physical or chemical changes through which these elements influence the heart beat little is definitely known. Calcium decreases and potassium increases the permeability of the cell mem-

brane. According to some, the excitability and contractibility of the muscle fiber is dependent upon the relative concentrations of H ions on the two sides of the cell membrane. The Ca and K ions through altering the cell permeability may in this way affect the diffusion of H ions across the membrane and so vary their relative concentrations on the two sides.

The effect upon the heart beat of changes in the reaction of the perfusion fluid

Acids when added in *moderate* excess act like potassium in that they favor relaxation of the cardiac muscle. The heart finally comes to rest in diastole. Alkalis, on the other hand, serve to prolong systole and shorten diastole. In this way they act like calcium. Acids depress and alkalis increase conductivity through the auriculo-ventricular bundle (p. 163). Andrus and Carter found that when the pH of the fluid perfusing the isolated mammalian heart was reduced to 7.0 complete heart block occurred (p. 213).

The higher tension of carbon dioxide during muscular exercise probably exerts a beneficial effect at this time upon cardiac behavior. During exercise the blood flow through the muscles is greatly augmented and a larger volume of blood is returned to the right side of the heart; the rise in carbon dioxide tension will favor more complete relaxation of the cardiac muscle for the accommodation of the greater load of venous blood.

The metabolism of cardiac muscle

From experiments in the past it had been concluded that the heart muscle derived energy by the direct utilization of blood sugar, since glucose disappeared from blood perfusing a heart-lung preparation, or from fluid used to perfuse the isolated heart. Figures ranging from 0.8 to 5.3 mg. per gram of heart muscle per hour have been obtained by different observers for the quantity of glucose removed by the heart. It has been shown, however, that a rapid breakdown of glucose (glycolysis) with the production of lactic acid occurs in blood after its removal from the body, i.e., free from contact with any tissue. Evans and his associates found that lactic acid was produced, as a result of glycolysis, at the rate of about 14 mg. per 100 cc. of blood per hour. Glycolysis also occurs in an artificial perfusion fluid as a result of bacterial action, and it has been shown that if rigid precautions are taken against bacterial growth, relatively small quantities of glucose disappear from fluid used to perfuse the excised heart.

The work of McGinty and of Lovatt Evans and their associates indicates that the heart muscle does not utilize glucose directly or does so to a minor extent. On the other hand, the heart removes relatively large amounts of lactic acid from the blood. McGinty and Miller analyzed the ingoing (arterial) and outgoing

(venous) blood of the coronary system of the beating heart *in situ*, and found that 0.39 mg. of glucose and 3.1 mg. of lactic acid per gram of heart tissue per hour disappeared. They concluded that glycolysis alone accounted for the loss of glucose none of which was actually absorbed by the heart muscle. Comparable results were obtained by Evans and his associates in their earlier experiments but in a more recent study they found that glucose was also consumed by the heart muscle though to a much less extent than was lactic acid. According to these workers, the blood lactic acid of the intact resting animal is derived from the breakdown of glucose in the lungs and in the blood itself. The lactic acid is removed, apparently oxidized, by the heart muscle and other tissues. During strenuous muscular exertion lactic acid is produced in large quantities in the active muscles and passing into the blood is removed in the same way (p. 619). Though glucose as well as glycogen and lactate is burned by the heart muscle, it is used mainly to restore the glycogen stores. Bogue and his associates found that the heart's glycogen store is rapidly depleted by the administration of adrenaline. The glycogen can be reformed again from glucose but not from lactate.

Fletcher and Waters, employing the heart-lung preparation perfused with heparinized blood containing no glucose (washed corpuscles in plasma previously fermented with baker's yeast) and a very low lactic acid concentration, found that in a heart performing moderate work over a 2 hour period no demonstrable reduction of the glycogen stores occurred, nor was there any diminution in the concentration of blood fat. From the results of other workers (Cruickshank and McClure) it appears that the mammalian heart does not utilize amino-acids as a source of energy to any important extent. The results of Fletcher and Waters' experiments indicate therefore that the heart can derive its sole energy requirements when necessary from non-carbohydrate material, most probably fat, composing its substance. These workers suggest that glycogen is used only as an emergency fuel, that is, when heavy work is undertaken. Evidence for the utilization of fat by the cardiac muscle has been furnished by the work of Cruickshank and McClure and by Visscher. Under certain conditions only a small fraction of the oxygen consumed by the heart can be accounted for by the oxidation of carbohydrate food (lactic acid and glucose), the balance being used presumably in the combustion of fat. On the other hand, with a high blood sugar the respiratory quotient (p. 523) may be 0.95 or 1.0, indicating a high carbohydrate utilization. The conclusion to be drawn from the results of the work of the various investigators in this field, is that the heart muscle shows a great adaptability in the utilization of different food materials. When lactic acid, glucose and fat are available all three may serve as sources of energy.

With regard to the chemical changes occurring in the cardiac muscle during activity, it may be said that for the frog's heart at least, and perhaps also for the mammal's, they are, in general, closely similar to those

taking place in skeletal muscle (p. 612). Phosphocreatine is broken down and lactic acid produced during anaerobic activity. The energy derived from the latter reaction is used for the resynthesis of phosphocreatine. In the recovery phase (diastole) a part of the lactic acid, it may be presumed, is resynthesized to glycogen and the remainder oxidized.

In the asphyxiated *frog* heart the phosphocreatine content of the muscle gradually diminishes and cardiac arrest occurs in about 15 or 20 minutes when all but about $\frac{1}{4}$ of the phosphocreatine store (which is only $\frac{1}{10}$ that of skeletal muscle) has disappeared. Readmission of oxygen brings about recovery and the restoration of the original phosphocreatine content. When poisoned with iodoacetic acid in the *absence* of oxygen, depletion of phosphocreatine occurs more rapidly, and the heart is arrested in from 2 to 4 minutes, but in the presence of oxygen the poisoned heart will continue to beat normally for an hour or so with no diminution of its phosphocreatine content. This indicates that the contractions of the frog's heart are not solely dependent upon the mechanism in the carbohydrate cycle upon which the drug acts (p. 614). All in all, phospho-

creatine would appear to be of much less importance as a source of energy for cardiac activity than for the contraction of skeletal muscle, the heart continuing to beat (provided that the lactic acid is removed by perfusion with an alkaline fluid) after its phosphocreatine content has been very greatly reduced. The mammalian heart (rabbit auricle) fails, however, when the phosphocreatine loss is much less. Yet the difference in this respect between the warm-blooded and cold-blooded hearts may be due simply to the former's greater frequency of beat (300 per minute of rabbit auricle) which is ten times that of the frog's heart. One would expect that, owing to the longer recovery period of the cold-blooded heart, it would not require such a large reserve of phosphocreatine. On the other hand, when the results of experiments on the amphibian and mammalian hearts are compared, several other discrepancies become apparent which suggest that the metabolism of the two may be fundamentally dissimilar; caution must be exercised in applying to the mammalian heart the chemical findings in experiments upon the heart of the frog.

CHAPTER XX

THE ORIGIN AND MODE OF TRANSMISSION OF THE HEART BEAT

If the heart of the frog is watched as it beats, waves of contraction may be observed to commence in the sinus region and pass over the auricle to the ventricle in orderly sequence. This wave of contraction is referred to as the beat of the heart. We know that the visible contraction is preceded by a measurable interval of time by an electrical change. Also, physico-chemical changes whose precise nature is unknown, undoubtedly precede or accompany the changes in electrical potential. These electrical and chemical changes which sweep over the heart in advance of the mechanical change are spoken of as the *cardiac impulse* or *excitation wave*.

HISTORICAL. Though Harvey (1628) studied the movements of the heart and discovered the circulation of the blood, he offered no explanation for the origin of the beat. Lower (1631-1691) thought that the beat was initiated by animal spirits which were supplied to the cardiac muscle through the vagus nerves. In the eighteenth century Haller, who observed that the spread of the contraction and the flow of blood through the chambers of the heart were events which proceeded hand in hand, concluded that the contact of the blood with the cardiac tissue at successive points was the direct stimulus for the muscular contraction. The contraction was looked upon as a simple peristaltic wave. Haller also pointed out that the right auricle was the last part of the heart to cease beating—the *ultimum moriens*—a fact consonant with his theory, since this chamber usually contained more blood at the time of death than other regions of the heart.

The latter view concerning the cause of the heart-beat was held until it was found that the excised heart would beat though its chambers were quite empty. It was then realized that whatever started the beat must arise within the heart itself. But other questions arose. Was the beat initiated by nervous tissue (ganglion cells) within the heart and carried to all its parts by nerve fibers or was the power of rhythmical contraction inherent in the muscle fiber? Two opinions have been held as to how these questions should be answered. One school, the *myogenic*, adhered to the view that the muscle fiber itself initiated the impulse. The other, the *neurogenic*, maintained that the impulse had its origin in nerve cells scattered among the muscle fibers and was conveyed for shorter or longer distances by nerve filaments. Support was given to the latter view by the discovery of three groups of ganglion cells in the frog's heart which were placed at what appeared to be strategic

points for the control of the beat. These groups of cells are known respectively as the *ganglia of Remak, Ludwig and Bidder*. The ganglion of Remak lies in the sinus venosus at its junction with the right auricle. Ludwig's ganglion is situated in the interauricular wall and Bidder's in the auriculo-ventricular groove. According to the neurogenic hypothesis Remak's ganglion was a nerve center which sent motor impulses to the cardiac muscle much as the respiratory center emits automatically a stream of impulses to the diaphragm and the other muscles of respiration. The other two centers were considered more or less subsidiary to this main one and to aid in the coordination of the beat.

THE FIRST AND SECOND STANNIUS LIGATURES. Stannius (1852) showed that if a ligature were tied tightly around the heart of the frog or turtle at the junction of the sinus with the auricle, the heart below the ligature ceased to beat though the rhythm of the sinus remained unaltered. After a time the auricles and ventricles recommenced to beat but at a different rate than the sinus. If while the ventricle was under the influence of the first ligature a second one were tied around the auriculo-ventricular groove the ventricle at once commenced again to beat. From the neurogenic point of view the following explanation seemed quite satisfactory. Stoppage of the auricles and ventricles by the first ligature was due to the injury sustained by the chief motor center—Remak's ganglion—and the removal of its influence. The second ligature re-established the ventricular beat by stimulating Bidder's ganglion. Yet an explanation based upon the myogenic conception was equally plausible. Impulses arising in the sinus musculature it was claimed were blocked by the compression of the first ligature. The auricular and ventricular muscles after a time resumed their beats spontaneously by virtue of their inherent power. The second ligature restored the beat by direct stimulation of the muscle in the auriculo-ventricular groove.

Gaskell (1881) showed that compression of the cardiac tissue not only at the sino-auricular junction, but anywhere between sinus and ventricle, as may be accomplished by a specially devised clamp (Gaskell's clamp), would cause standstill of the heart below. This is so though the tissue between the jaws of the clamp is devoid of nervous elements. The part below the clamp later commences to beat at a rate of its own. Gaskell also found that gradual compression of the tissue in the auriculo-ventricular groove stopped the contractions of the ventricle. If the ganglion cells in this region (Bidder's) were then stimulated by a needle no contractions were called forth. On the other hand,

when the muscular tissue, free from nerve cells, was pricked rhythmical beats followed. It has also been shown that the tissue of the great veins which contain no ganglion cells exhibits spontaneous rhythmicity when completely separated from the sinus. Furthermore, in the heart of the tortoise it is possible to separate the sinus and the ventricle, except for a narrow bridge of muscular tissue and a single nerve (the coronary nerve). The only nervous communication between the two chambers is by means of this nerve. If in a heart so prepared the coronary nerve be cut no change in the rhythms of sinus and ventricle occurs. On the other hand, if the nerve trunk be left intact but the muscular connection severed, the two chambers then beat quite independently of one another.

From the results of these experiments it was difficult to draw any other conclusion than that the beat of the primitive heart was myogenic. Gaskell also showed that muscular tissue in different regions of the heart possessed rhythmical powers of varying degrees. The sinus was shown to possess the greatest rhythmical power; the auricle in the region of the auriculo-ventricular junction was endowed with less and the ventricle with the least. The sinus, it was believed, originated the beat under ordinary circumstances, from here the impulse spread through the muscular tissue to the other regions of the heart. Though the sinus usually dominated the rhythm of the heart another region could, upon occasions when the function of the sinus was depressed, usurp control and develop a beat of its own.

Apparently there was no obstacle to the acceptance of the myogenic conception in so far as the amphibian or the reptilian heart was concerned, since in them the musculatures of the auricles and ventricles are continuous across the auriculo-ventricular groove. But the muscle tissue in these regions of the mammalian heart was apparently completely separated by the auriculo-ventricular ring of connective tissue. In the face of this fact there was no alternative but to believe that the transmission of the beat in higher animals was mediated by nerve fibers; and if this were so its origin in nervous tissue also must be granted.

The foregoing objection to the application of the myogenic theory to the mammalian heart was removed by the work of Kent who demonstrated the existence in rats of muscle fibers passing through the connective tissue of the A-V ring. Shortly afterwards His described in other mammals a definite bundle of primitive muscular tissue (bundle of His, or auriculo-ventricular bundle) connecting the right auricle and the ventricles. This bundle and the nodes of similar tissue in the right auricle will be presently described.

In addition to the evidence just given the following facts in favor of the myogenic theory of the origin of the beat may be cited. (a) In the embryo chick the rudimentary heart shows rhythmical contractions after 36 hours. Ganglion cells do not appear until after the 6th day. The heart of the human fetus commences to beat after 3 weeks of gestation; nervous elements do

not appear until 2 weeks later. (b) The muscular tissue of the apex is said to be free from ganglion cells yet a strip excised from this region beats rhythmically. (c) If zig-zag cuts be made in the ventricle so as to interrupt any nervous paths of transmission that might exist, the sequence of the beat is unaffected. (d) In several invertebrate hearts no ganglion cells can be demonstrated.

THE SPECIALIZED TISSUES OF THE MAMMALIAN HEART

The muscle fibers mentioned in the foregoing section which were discovered by Kent to form connections between the auricles and ventricles have subsequently been shown to belong to and form part of a special system for the origin and propagation of the beat in the mammalian heart. This system is composed of primitive muscle tissue interspersed with nerve cells and fibers. There is every reason to believe, however, that the initiation of the beat in, and its transmission through this system depends upon its muscular elements.¹

These specialized tissues comprise the following structures, (fig. 59).

The sino-auricular node

The auriculo-ventricular node

The auriculo-ventricular bundle

The branches of the bundle and the Purkinje system

(1) *The sino-auricular (S-A) node*

The sino-auricular node was discovered by Keith and Flack in 1907. It lies embedded in the muscle of the right auricle to the left of a slight ridge situated on the inner surface of the chamber and known as the *tenia terminalis*. The tenia corresponds to a shallow groove on the outer surface of the auricle—the *sulcus terminalis*—which runs downwards from a point to the right of the opening of the superior vena cava to the inferior caval opening. The situation of the node in relation to the outer surface of the auricle is therefore to the left of the upper part of the sulcus terminalis and just in front of the opening of the superior vena cava. The node extends downwards for about $\frac{1}{2}$ of an inch. It has a special blood supply. Its

¹ The muscle cells have been shown to be capable of rhythmical contraction. Also if the continuity of the tissue be interrupted the gap is subsequently bridged over with scar tissue. Regeneration does not occur and conduction is never restored; this is contrary to what one would expect if the pathway of conduction were composed of nervous tissue. When the intestine, for instance, is cut across and the cut ends sutured together the divided fibers of Auerbach's plexus regenerate and functional continuity between the nervous elements in the two segments is soon restored.

minute structure is of a neuromuscular nature consisting of striated spindle-shaped muscle fibers arranged in a plexiform manner, embedded in connective tissue and intermingled with a small number of ganglion cells and nerve fibers.

Knowing the ancestry of the node, which we shall see can be traced from the sinus tissue of the primitive heart, we may suspect its function. Just as the sinus initiates the beat and sets the pace for the cold-blooded heart so the S-A node is the *pacemaker* of the mammalian heart. There exists for this statement, however, more than presumptive evidence based upon embryological considerations. The direct experimental evidence will be considered later.

(2) *The auriculo-ventricular (A-V) node*

This was first described by 1906 by Tawara. It lies in the right auricle at the lower part of the interauricular septum, anterior to the opening of the coronary sinus and above the septal leaf of the right auriculo-ventricular valve. Its microscopical structure closely resembles that of the S-A node. Its power of impulse formation is apparently second only to that of the latter. When the S-A node is destroyed or its function depressed the A-V node may then assume the duties of pacemaker. Ordinarily a definite time interval exists between the beginning of auricular and ventricular systoles. When the A-V node initiates the impulse the interval is much shorter or may be abolished, both chambers contracting nearly or quite simultaneously, since the impulse reaches both at practically the same time. This is spoken of as *nodal* rhythm and occurs as a clinical disorder (p. 194). The S-A and A-V nodes are apparently unconnected by any tract of special tissue the two being completely separated by auricular muscle. The primitive muscle cells of both nodes make intimate connection with the surrounding muscle fibers through the intermediary of cells which are transitional in structure between those of the nodal and auricular fibers.

(3) *The auriculo-ventricular bundle, and (4) Bundle branches and Purkinje system*

It was mentioned on page 162 that following the discovery by Kent of muscular bridges connecting the auricle with the ventricle a well defined bundle of muscular tissue was described by His. This bundle runs a short horizontal course forward and to the left from its origin at the A-V node, passing over the septal leaf of the tricuspid valve to the

upper part of the interventricular septum. Here it divides into a right and left branch, each going to the corresponding ventricle. The ventricular divisions pass downwards beneath the endocardium of the septum and give off primary branches to the papillary muscles. The strands are continued beneath the lining of the ventricle and divide into innumerable filaments to form a delicate subendocardial interlacement. The muscle cells composing the ventricular branches and terminal arborizations of the system take on very special features, differing from those of the bundle stem and of the auriculo-ventricular node. The cells are much larger than in the latter situations, having a swollen appearance with large pale nuclei. These peculiar cells were described by Purkinje and had been known by his name long before their significance was recognized. Tawara's researches showed that such cells constituted the ventricular continuation of the bundle. Nervous elements are also seen among the Purkinje fibers. The anatomical researches of Abramson and associates have shown that the Purkinje system does not consist simply of a layer of interlacing fibers beneath the endocardium, as has been supposed, but penetrates deeply into the ventricular muscle.

The auriculo-ventricular bundle and its branches are demarcated from the adjacent cardiac tissue by a fairly well defined connective tissue sheath. Lhamon injected the sheath with colored fluids and found that the stem and branches were completely invested even to the finer terminations, also septa were found penetrating between the fibers to enclose individual Purkinje fasciculi.

THE DEVELOPMENT OF THE JUNCTIONAL TISSUES. The heart of lower vertebrates (frog, turtle, etc.) and the heart of the mammalian embryo possess an extra chamber—the *sinus venosus* (a, in fig. 60) which first receives the blood from the veins before it enters the auricle. In the early embryo two veins conveying blood chiefly from the upper part of the body and termed the right and left ducts of Cuvier open into the sinus. The blood passes from the sinus through an opening guarded by the *right and left venous valves* into a small ill-defined chamber, the *auricular canal* (b). The latter opens into the auricle above. Below where it forms a ring around the auriculo-ventricular junction, it is invaginated or telescoped into the ventricular cavity. This portion serves the purpose of a muscular bridge for the transmission of the impulse between the auricle and ventricle in the cold-blooded heart (p. 162). In the course of development of the mammalian heart these embryonic structures disappear but the tissue of which they are composed is believed to persist in vestigial form as the system of specialized structures

already described, namely, the sino-auricular node and the auriculo-ventricular node and bundle.

The developmental history of these several parts of the system is as follows:

(a) The line of junction of the sinus venosus with the primitive auricle is represented by the sulcus terminalis of the adult heart. The tissue of the wall of the sinus at the opening of the right duct of Cuvier (which enters into the formation of the superior vena cava) and the tissue comprising the right venous valve are represented in the adult heart by the sino-auricular node.

(b) The sinus wall in the region of the left duct of Cuvier (which becomes in part the coronary sinus) and

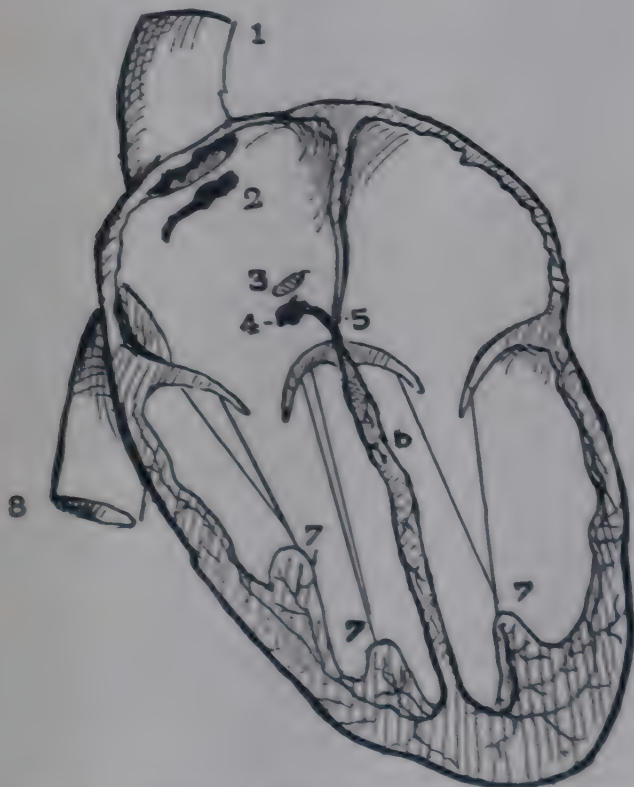


FIG. 60. Diagram representing the junctional tissues of the mammalian heart. 1. Superior vena cava, 2. sino-auricular node, 3. coronary sinus, 4. auriculo-ventricular node, 5. auriculo-ventricular bundle, 6. primary branches of bundle, 7. papillary muscles, 8. inferior vena cava.

the tissue of the left venous valve remains as the auriculo-ventricular node.

(c) The funnel-shaped invagination of the auricular canal is represented in the adult heart as the auriculo-ventricular bundle.

The investigations of Keith and Mackenzie suggest that the parts of the cold-blooded heart (sino-auricular and auriculo-ventricular junctions) from which the junctional tissues of the mammalian heart have apparently evolved are also of specialized neuromuscular structure (nodal tissue). According to these observers this explains the greater rhythmicity of these regions of the cold-blooded heart. The tissue is more diffuse in the hearts of lower orders, forming in these incomplete rings at the sino-auricular and auriculo-ventricular junctions, whereas in the mammal it is more localized.

The condensation becomes more pronounced as the animal scale is ascended.

EVIDENCE FOR THE ORIGIN OF THE CARDIAC IMPULSE IN THE SINO-AURICULAR NODE

(1) Heat or cold applied locally to the node, but not to other parts of the heart, causes increase or decrease, respectively, in the rate of the heart beat.

(2) Destruction or excision of the node causes the rest of the heart to stop beating for a time. Such procedures are analogous to the first Stannius experiment as performed upon the cold-blooded heart. Cohn, Kessel and Mason investigated the subject very fully in perfused hearts both inside and outside the body. They found that excisions of portions of tissue in the region of the node merely accelerated the rate. Incisions separating the node on three sides did not block the impulse. The beat ceased, however, upon completion of the rectangle by a fourth incision. The resumption of the beat in the auricles and ventricles was at a slower rate after the immediate effect of the incision (complete stoppage for from 4 seconds to 3 minutes) had passed off.

(3) In a case of complete ectopia cordis in man, the impulse has been observed to originate in the region of the sino-auricular node, and to spread uniformly from there through the auricles. The apex of the heart becomes excited slightly ahead of the base.

(4) It was shown by Lewis that a contraction induced by artificial stimulation gave an electrocardiogram (p. 180) which most closely simulated the normal when the stimulus was applied in the vicinity of the S-A node itself. Abnormal P waves appeared when any other part of the auricle was excited.

(5) The crucial experiment proving the initiation of the beat in the S-A node was devised by Lewis. By means of a pair of contacts placed in different positions upon the surface of the normally beating heart of the dog, and connected with a galvanometer Lewis demonstrated that at each beat the node was the first part of the heart to show relative negativity. (See Fig. 60A.)

In order to understand this piece of evidence it is necessary to recall some of the fundamental principles of the electro-physiology of muscle. In figure 61 I, A and B represent opposite ends of a muscle strip. Contacts placed on each end of the muscle are connected with a galvanometer, and the polarity of this is such that when B is negative to the rest of the muscle the galvanometer mirror

swings to the right, and a beam of light thrown upon a moving photographic surface causes an upright wave (positive wave) to be traced. When A is negative a reverse movement occurs and a curve is inscribed below the base line (negative wave). The two ends of a muscle at rest and uninjured have equal electric values and the galvanometer needle remains stationary when the contacts are placed in these situations. Excited or injured muscle is, however, relatively negative to muscle in the non-excited or uninjured state. When, therefore, B in figure 61 I, 1 is stimulated electrically or otherwise the muscle at that point becomes relatively negative to the rest of the muscle, a current flows within the strip in the direction of the

auricle which first became negative (primary negativity) was the S-A node. Consequently the impulse must originate within it. Contacts placed upon the beating heart always gave maximal deflections when they were situated along a line representing the radius of a circle having the S-A node as its center. Further, when the contacts were placed between the node and the ventricles—their order and the polarity of the galvanometer being as described above,—the initial deflection was upward. Finally, when one contact was placed precisely upon the node and the other placed at any point in the circumference of a circle surrounding the first, the deflections were always maximal and the first one directed upward.

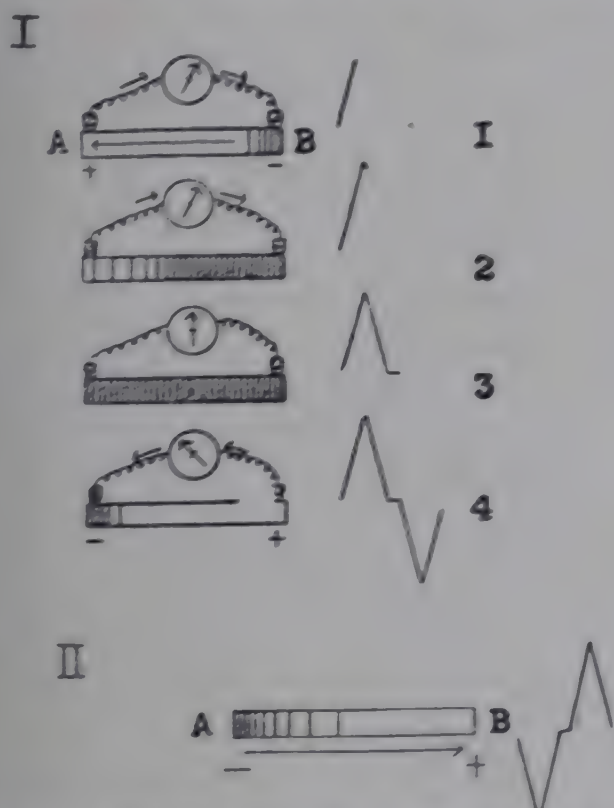


FIG. 60A. Modified from Lewis. Description in text.

arrow, and a stroke above the base line of the tracing is inscribed. When the potential change associated with the excitation wave has spread over the muscle strip (fig. 61, I, 2 and 3) and involved that portion beneath contact A, the potential of the two ends is the same. The curve reaches the base line and follows it for a short distance, corresponding to the time during which this state of equal potential (isopotential) persists. The excitation wave retreats from the strip in the same order that it advanced. This, of course, will cause A, while it remains in the excited state, to become negative relatively to B. The direction of current flow will now be reversed and a wave below the base line will be inscribed (4 in figure).

Applying this method to an investigation of the auricle itself Lewis found that the region of the



FIG. 61. A generalized type of vertebrate heart—combining features found in the eel, dogfish and frog (Keith); a, sinus venosus and veins; b, auricular canal; c, auricle; d, ventricle; e, bulbus cordis; f, aorta; 1-1, sino-auricular junction and venous valves; 2-2, canalo-auricular junction; 3-3, annular part of auricle; 4-4, invaginated part of auricle; 5, bulbo-ventricular junction R.D.C. and L.D.C., right and left ducts of Cuvier, (after Keith).

THE SPREAD OF THE EXCITATION WAVE THROUGH THE HEART

The transmission of the excitation wave from the sino-auricular to the auriculo-ventricular node

The impulse is transmitted to the A-V node and across the inter-auricular septum to the left auricle through the muscular tissue. It spreads at practically equal rates in all directions; there is no tract of specialized tissue offering a pathway of "least resistance" to the auriculo-ventricular node. On this account it is difficult to produce a complete auricular blockage of the impulse. The practical uniformity of the transmission rates along different paths radiating up or down to the right or left from the S-A node has been clearly demonstrated by Lewis. Contacts were placed in series upon the

surface of the auricle or upon the great veins and the arrival of the impulse at different points accurately timed. The spread upwards through the wall of the superior vena cava was found to be an exception to the general rule, the rate being somewhat slower than in other directions. Lewis has shown that the equality of the transmission rates through the auricle has an anatomical basis. The S-A node holds a strategical position in relation to the auricular musculature. The chief muscle bands of the right auricle radiate from the region immediately below the node, termed the *concentration point*, like the sticks of a Japanese fan. The average rate of propagation of the excitation wave through the auricular muscle is 1000 mm. per second.

The transmission of the impulse from auricle to ventricle

The auriculo-ventricular node, which we have already seen forms intimate connections with the auricular fibers, forms the first link in the chain which transmits the impulse to the ventricle. The bundle, its right and left branches and the terminal arborizations of the latter constitute the rest of the transmission system. *In the mammalian heart the bundle is the sole path by which the cardiac impulse can be conveyed from auricle to ventricle.* Several investigators have demonstrated this fact conclusively by simply cutting or crushing the narrow bridge of special tissue. This is invariably followed by complete dissociation of auricular and ventricular rhythms. The cardiac disorder produced in this way is spoken of as *complete experimental heart block*. Erlanger and Blackman crushed the bundle in dogs under aseptic conditions by a specially devised clamp (Erlanger clamp). The animals lived from 320 to 340 days and during this time showed complete heart block. These experimenters showed what had not been shown before, that no other tissue could take over the duties of the bundle though the period of survival was sufficient, were it possible for such a vicarious action to be exercised. The experiment also shows that regeneration of the bundle does not take place. Epileptiform and syncopal attacks were observed in some of the animals. This is of much interest in view of the occurrence of similar manifestations in man as a result of disease of the bundle (see heart block, p. 190).

The two ventricles do not contract exactly simultaneously. Sometimes one, sometimes the other chamber precedes its fellow by one or two hundredths of a second. The interval between the

excitation of the auricles and the ventricles (A-V interval) has a duration in the human heart of between 0.012 and 0.020 seconds. The most widely accepted theory of this delay in the spread of excitation to the ventricles is the slower conduction rate of the junctional tissue (A-V node and bundle). Another view is that the delay is due to the latency of the response of the ventricular muscle or of the A-V node to the auricular impulses. Abnormally long A-V intervals (over 0.20 seconds) constitute the condition known as heart block (p. 190). Very rarely, shortening of the A-V interval to less than the lower normal limit occurs. It is due, in all probability, to the existence of an aberrant or accessory auriculo-ventricular bundle.

The spread of the excitation wave in the ventricle

The transmission of the impulse to the various regions of the ventricular musculature, right and left, is entirely by way of the His-Tawara system. Just as compression or section of the stem of the bundle causes complete functional dissociation of auricle and ventricle, so injury to one of the main (septal) branches interferes with the passage of impulses to the corresponding ventricle (p. 185, 190). The excitation wave after traversing the main branches follows the fine arborizations of the Purkinje pathway lying beneath the endocardium, and so completes a semicircular journey in each ventricle from the upper part of the interventricular system to the base of the heart. This takes 0.04 second and is at a rate of about 5000 mm. per second.

The mode of transmission of the impulse throughout the ventricular muscle is a question which has not received a final answer. Lewis' experiments indicated that the spread of the excitation was entirely through the Purkinje network lying beneath the endocardium, the impulses being then transmitted radially, i.e., by the most direct course, through the overlying ventricular muscle to the epicardial surface (see fig. 75, p. 185). In other words, the impulses, according to Lewis, did not follow the course of the muscular bundles of the heart, but cut across them by the most direct path from the endocardial to the epicardial surface. Robb and her associates, on the contrary, maintain that the impulse is transmitted from the main divisions of the Purkinje system through muscular tissue, following the direction of the muscle bundles. Abramson and others dissent from the latter view, claiming that the excitation wave reaches the individual muscle fibers via the myocardial exten-

sions of the Purkinje system (p. 163). The muscle fibers in numerous places are thus excited almost simultaneously.

The facts detailed in this chapter concerning the origin and spread of the excitation wave may now be summed up. The beat is initiated in the tissue of the sino-auricular node. From here it is "broadcast" through the auricular musculature with practically equal velocity in all directions. The A-V node acting, so to speak, as a relay station, receives the impulse and transmits it to the

ventricle via the auriculo-ventricular bundle. At the upper part of the interventricular system the pathway forks and the wave of excitation reaches each ventricle simultaneously. Its further course is through the branches of the bundle and its terminal arborizations. The mode of spread of the impulse to the ventricular muscle fibers is a debated question, but is probably through the myocardial extensions of the Purkinje system; thus different parts of the muscle are excited almost simultaneously.

CHAPTER XXI

THE CARDIAC CYCLE

GENERAL DESCRIPTION

The succession of changes which occurs in the heart and is repeated during each beat is referred to as the *cardiac cycle*. On account of the rapidity with which the events in the cycle follow one another, it is impossible to study them by mere inspection. Harvey remarked upon the difficulties of the problem.¹ Modern methods of study include the graphic registration of pressure changes within the auricles and ventricles in animals, i.e., *intra-auricular* and *intra-ventricular pressure curves*. In man, records of the *arterial* and *venous pulses* (p. 188) obtained by means of the *polygraph* or of the electrical changes—*electrocardiograms*—(p. 181) are employed in the study of cardiac action.

Before studying the intracardiac pressure curves and the methods by which they are obtained, a general account of the several phases of the cycle and their approximate time relations will be given. The contraction and relaxation of the auricles are called *auricular systole* and *auricular diastole* respectively. *Ventricular systole* and *ventricular diastole* refer to corresponding phases of the ventricular muscle. The length of the cardiac cycle, when the heart is beating at the usual rate (70 per minute), is $\frac{2}{3}$ of a second (0.86 second). Its duration, of course, varies inversely with the heart rate. The moment in the cycle when ventricular systole has just come to an end, may be chosen as the most convenient starting point for a description of the succession of events. At this time, the auricles and ventricles are relaxed. Blood is pour-

ing into the cavity of the right auricle from the venae cavae and into the left auricle from the pulmonary veins. The auricular and ventricular cavities are separated from one another by the closed auriculo-ventricular valves. The semilunar valves also have been brought into apposition, so, during this period (0.08 to 0.12 second) the ventricles are completely closed but almost empty chambers. The auricles, on the other hand, are filled with blood which has accumulated during the previous ventricular contraction, but, as the pressure in the ventricle falls below the intra-auricular pressure, the auriculo-ventricular valves are opened; venous blood under a pressure of a few millimeters of water then pours into the fully relaxed ventricles. The latter chambers continue to fill throughout the remainder of diastole, that is, for about 0.40 second, nearly half the total length of the cardiac cycle. Toward the end of ventricular filling, however, the auricle contracts and the flow into the ventricle is hastened. The right auricle contracts slightly (0.013 sec.) before the left. Auricular systole lasts for 0.1 second. As a rule no interval or a very short one (0.016 second) elapses between the end of auricular and the commencement of ventricular systole. The fall in pressure in the auricle consequent upon its relaxation, and the rise of pressure within the ventricle as it contracts closes the A-V valves. The ventricle is again for a time (0.04 to 0.06 second) a closed cavity, since the semilunar valves have not yet opened. During this period the intraventricular pressure rises rapidly. The semilunar valves are forced open and the blood is discharged into the aorta and the pulmonary artery. The pressure continues to rise but soon reaches a maximum and is maintained around this level for a short time. The ventricle then enters upon its relaxation phase; the pressure falls and the semilunar valves close again. This brings us around to the point from which we started; a cardiac cycle has been completed.

Emphasis should be laid upon the following points in the foregoing description.

(a) Blood pours into the auricles throughout the entire cycle except for the short period (0.1 second) occupied by auricular systole.

(b) Filling of the ventricle continues throughout

¹ "When I first tried animal experimentation for the purpose of discovering the motions and functions of the heart by actual inspection and not by other people's books, I found it so truly difficult that I almost believed with Fracastorius, that the motion of the heart was to be understood by God alone. I could not really tell when systole or diastole took place, or when or where dilatation or constriction occurred, because of the quickness of the movement. In many animals this takes place in the twinkling of an eye, like a flash of lightning. Systole seemed now here, now there; diastole the same; then all reversed, varied and confused. So I could reach no decision, neither about what I might conclude myself nor believe from others. I did not marvel that Andreas Laurentius wrote that the motion of the heart was as perplexing as the flux and reflux of Euripus was to Aristotle." William Harvey, "Exercitatio anatomica de motu cordis et sanguinis in animalibus," 1628.

the cycle except during its contraction and the brief succeeding period (0.08 second) which intervenes between the closure of the semilunar and the opening of the A-V valves.

(c) The ventricle contracts for about 0.30 second and rests for about 0.50 second. The auricle contracts for 0.1 second and rests for 0.7 second. The resting periods of the two chambers therefore overlap for a period (about 0.40 second) during which the whole heart is quiescent.

The following table gives the approximate figures for the duration of the chief phases of the cardiac cycle when the heart is beating at the usual rate of 70.

	seconds
Ventricular systole.....	0.3
Ventricular diastole.....	0.5
Auricular systole.....	0.1
Auricular diastole.....	0.7
Quiescent period of whole heart.....	0.4

THE GRAPHIC REGISTRATION OF INTRA-CARDIAC PRESSURES

The times of filling and emptying of the cardiac chambers, the pressures developed and the times of opening and closing of the valves guarding the orifices of the heart can be studied with great precision by this method.

MANOMETERS. The pressure changes within the heart cavities are recorded by means of optical manometers. A mercury manometer, owing to the great inertia of the column of metal, and the rapid changes in pressure which take place during the cardiac cycle, is unsuitable. The pressure in the left ventricle, for example, reaches a value of 100 mm. Hg or more within a few hundredths of a second. On account of the lag of a mercury column the amplitude of the curve obtained by a mercury manometer is considerably less than it should be, and the recorded pressure is, in consequence, less than that which actually exists; also, minor fluctuations in pressure are not registered. Tambours covered with a thin rubber membrane, upon which a light lever is fixed, have been employed with the view of overcoming these disadvantages. Marey's instrument is based upon this principle. In Hurtle's instrument, on the other hand, the pressure changes are made to bend a stiff spring, and in Fick's the curvature of a tubular spring is altered by pressure changes transmitted to its cavity. The moving parts of all these types, however, possess considerable mass and, though improvements over the mercury manometer, tend, nevertheless, through their inertia to cause inaccuracies in recording. In the *optical method* an imponderable lever, namely, a beam of light, is employed. The movements of the beam of light are recorded photographically. This

and the other methods just referred to must, of course, be calibrated against a mercury column in order to ob-

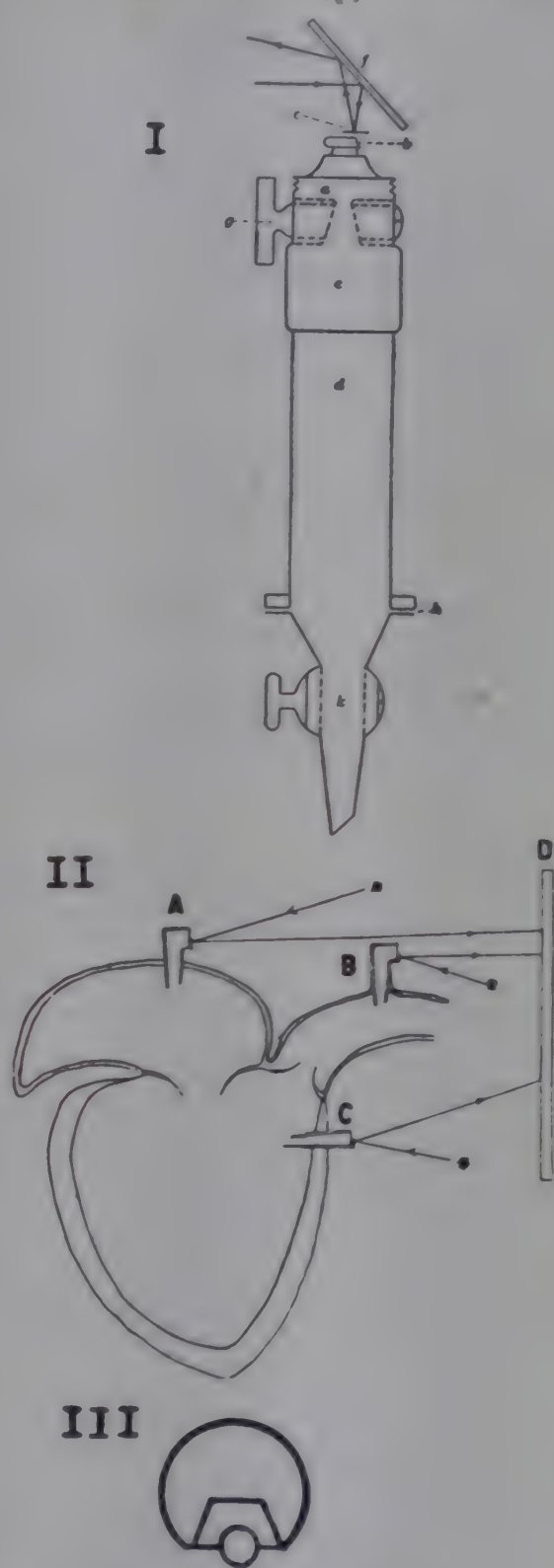


FIG. 62. I. Optical manometer for registering intra-cardiac pressure. *a*, damping plate; *b*, segment capsule; *c*, small Zeiss mirror; *d*, glass tube; *e*, brass cylinder; *f*, reflecting mirror; *g*, stopcock; *h*, conical joint for attaching different types of cannula. II. Diagram to illustrate optical method of recording. *A*, manometer in auricle; *B*, in aorta; *C*, in ventricle; *D*, photographic surface. III. Enlarged view of segment capsule, see text (after Wiggers, in part redrawn).

tain quantitative results. A description of Wigger's modification of Frank's optical method follows.

The instrument (fig. 62, I and II) consists of (1) a glass tube which is introduced into the ventricle, the auricle or the aorta. The tube is surmounted by a

brass chamber (c) which can be connected or disconnected with the lower part of the tube by means of a stopcock (g), and the pressure thus transmitted to the recording part of the apparatus as required. (2) A segment capsule (b) carrying a small mirror closes the brass chamber above. (3) a moving photographic surface—plate or film.

The segment capsule (fig. 62, III) consists of a small chamber 3 mm. in diameter and circular in cross section except that a segment with a small arc has been cut off one side. The chamber is covered with a tightly stretched, thin rubber membrane. A small trapezoid celluloid plate is cemented to the surface of the membrane with the longer of its unequal sides lying flush with the chord of the capsule, while its shorter side does not extend as far as the center of the circle. The mirror is cemented in turn to the celluloid plate with its center lying precisely over the chord of the capsule upon which it pivots. By means of this device, changes in pressure transmitted to the membrane cause movements of the mirror which are greater than those of the membrane itself. The instrument is firmly clamped in position and a strong light focused upon the mirror.



FIG. 63. Auricular pressure curve. Description in text.

The beam is reflected to a second larger mirror which is adjusted to bring the ray into the horizontal plane, and have it fall ultimately upon a photographic surface moving in a suitable camera (photokymograph) across the path of the beam. The longer the beam the greater, of course, will be the magnification, though there is a limit to the length (120 to 150 cm.) which can be used advantageously.

THE INTRA-AURICULAR PRESSURE CURVE

This shows three crests (positive waves) *a*, *c*, and *v* and three depressions (negative waves) *x*, *x'*, and *y* (see fig. 63). The *first positive wave*, *a*, is caused by auricular systole. It rises fairly steeply to its summit but only represents a pressure of a few millimeters of mercury. It should be pointed out that all parts of the auricular muscle do not contract together but progressively with the spread of the excitation wave. During the rise in the *a* wave more and more fibers are entering into the excited state, tension is being developed and the auricular pressure is rising. At the summit of *a* all fibers are contracting. After this, the fibers relax also in a progressive fashion, those first excited being the first to relax and the pressure falls. The subsequent decline in pressure produces

the "negative" wave, *x*. Wiggers refers to the time during which a group of fibers remains in a contracted state as the *fractionate contraction*. The shortening of the auricular muscle as a whole is the resultant of the contracted and the relaxations. So he divides auricular systole in two phases, a *dynamic phase*, in which the proportion of the muscle fibers in the contracted state increasing and the pressure is rising to a maximum and an *odynamic phase* in which the pressure falling as a result of the fractionate contraction coming to an end in progressively greater number. The duration of each phase is about 0.05 second.

The *second positive wave*, *c*, is due to the rise in pressure in the ventricle as this chamber commences its contraction. The pressure is transmitted to the auricle through the closed A-V valves which are bulged into the upper chamber. The summit of *c* coincides with the opening of the semilunar valves.

The decline of the *c* wave and the production of the *negative wave*, *x'*, is ascribed to two factors: (a) the increase in the negative pressure within the thorax resulting from the ejection of the ventricular contents—about 60 cc. in man—from the thoracic cavity, (p. 157) (b) the drawing down of the auriculo-ventricular septum as the ventricle contracts.

The *third positive wave*, *v*, is a stasis wave. It is due to the inflow of blood from the veins and accumulation in the auricle while the A-V valves are closed. It is therefore the result indirectly, is the *c* wave, of ventricular systole.

The decline of wave *v* and the production of *negative fluctuation*, *y*, are due to the opening of A-V valves and the escape of the blood into the relaxed ventricle. A small notch which sometimes appears on the upstroke of the *v* wave near its summit is ascribed to a vibration set up by closure of the semilunar valves.

The pressure curves of the two auricles show similar features but are not perfectly synchronous. As a result of the time taken for the excitation wave to spread to the left auricle, systole of this chamber commences 0.013 second after that of the right.

The auricular contraction would appear to be of minor importance in the dynamics of the circulation, i.e., in the filling of the ventricle. This may be evident when it is recalled that the dynamic phase of auricular systole occupies only 0.05 second while the total period of ventricular filling has a duration of about 0.4 second. Also in auricular fibrillation (p. 187) in which condition the au-

certainly exert no propulsive force upon the blood, filling of the ventricle is apparently not interfered with.

THE INTRA-VENTRICULAR PRESSURE CURVE

The auricle and ventricle throughout a large part of the cardiac cycle communicate with one another through the A-V opening, the pressures in the two cavities during this time are therefore practically equal. When auricular and ventricular pressures are recorded simultaneously the two

curves of the curve is inscribed. Upon attaining a value in each ventricle just greater than the aortic or pulmonary diastolic pressure, respectively, the semilunar valves are forced open. This point is marked by line 2 in figure 64. The ventricular cavities and arterial lumina are now in free communication with one another, the ventricular and arterial pressures are practically equal and continue to rise together for a time, but soon reaching their maxima, forms the short plateau or rounded summits of the curves. A sharp decline in the

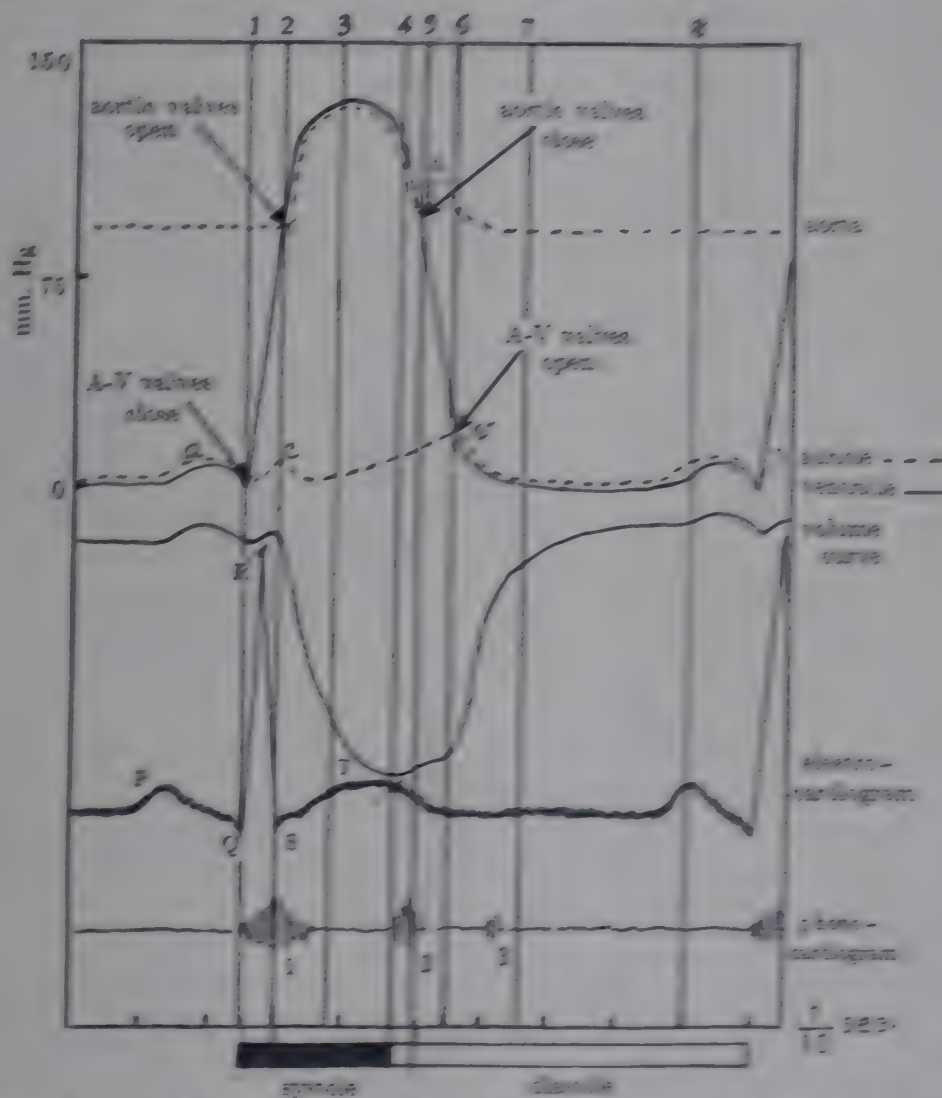


Fig. 64. Superimposed curves of ventricular, auricular and aortic pressure, together with a ventricular volume curve, an electrocardiogram and a phonocardiogram (see text).

curves run parallel for long stretches (fig. 64). A small positive wave is frequently seen just preceding the main pressure rise of the ventricular curve (line 8). This occurs synchronously with the c wave of the intra-auricular curve and is due to auricular systole. When the ventricle contracts (line 1) the pressure rises rapidly and almost immediately mounts above the auricular pressure. This causes the firm closure of the A-V valves (line 3), as we have seen, actually bulge into the ventricular cavity to produce the c wave. The pressure continues to rise and the steep upstroke

of the curve follows as systole comes to an end and the ventricular muscle commences to relax. The fall in intra-ventricular pressure below the aortic pressure causes the closure of the semilunar valves (line 5). This sharp drop in pressure at the termination of systole produces the incisura of the central arterial pulse (p. 153).

Following the closure of the valves and as a result of the more complete relaxation of the ventricle the pressure curve falls precipitously to finally reach a level below the auricular pressure (line 6). At this instant the A-V valves open and

blood is again received from the upper chamber. Throughout the period which follows in which both auricle and ventricle are relaxed, pressures in the two cavities are approximately equal and at a low level. Toward the latter half of this period, however, the curves may show a gradual rise as a result of the distension of the heart cavities by the accumulated blood and the rise in venous pressure.

THE PHASES OF THE CARDIAC CYCLE AS SHOWN BY THE VENTRICULAR PRESSURE CURVE

The vertical lines numbered from 1 to 8 drawn through the ventricular curve indicate the occurrence of important events in the cardiac cycle. When, as in the figure, arterial, auricular and venous pulse tracings are accurately superimposed with the ventricular curve, that is, when all tracings commence at the same instant and are inscribed beneath one another, then the numbered lines will indicate synchronous events in the various curves at the points of intersection.

The phases of ventricular systole and the post-sphygmic period of ventricular diastole

Ventricular systole is represented by that part of the pressure curve included between lines 1 and 5. That is, from the closure of the A-V valves to the closure of the semilunar valves. In man while the body is at rest, the entire length of ventricular systole is about 0.30 second (from 0.25 to 0.36 second). Its length varies with the pulse rate, shortening with acceleration of the heart, and vice versa. Systole is divided into two periods by the opening of the semilunar valves (line 2). The first of these phases (from line 1 to line 2) is termed the *presphygmic period* or *period of isometric contraction*. The former term implies that this period precedes the appearance of the arterial pulse (sphygmus = pulse); the latter term connotes that the muscle fibers are not shortening. This is actually the case, since the fibers are at this time contracting upon a mass of liquid which is incompressible and completely fills a closed cavity. The second phase (line 2 to line 5) intervenes between the opening and closing of the semilunar valves and is termed the *sphygmic* or *ejection period*, since during this time the blood is being discharged into the aortic and pulmonary arteries. The short period of ventricular diastole immediately following the ejection period and up to the moment of opening of the A-V valves (line 6) is known as the *post-sphygmic period* or *period of isometric relaxation*. During this period the ventricle is again closed and undergoing relaxation, no blood is

entering its cavity so that the length of the fibers remains unchanged—hence the use of the latter term.

In man the presphygmic or isometric contraction period lasts for from 0.04 to 0.06 second. It is subject to little variation under changing conditions of heart rate, etc. The period of ejection takes up the balance of the time of the systolic period, i.e., about 0.25 second. Variations in the length of systole associated with changes in heart rate are brought about chiefly by changes in length of the ejection phase. The latter is prolonged in aortic stenosis.



FIG. 65. Diagram of cardiac cycle. A.S., auricular systole; I.C., period of isometric contraction; M.E., period of maximum ejection; R.F., period of reduced ejection; P., protodiastolic period; I.R., period of isometric relaxation; R.F., period of rapid filling; D., period of diastasis. Divisions of outer circle represent tenths of seconds.

The commencement of the period of isometric contraction is synchronous with the initial vibrations of the first heart sound and follows by a small fraction of a second the beginning of the R wave of the electrocardiogram (p. 181). The termination of this period and the commencement of ejection is marked by the rise in the arterial pressure curve. The end of the ejection period coincides with the beginning of the second heart sound. Therefore, the total duration of systole may be determined in man from the interval elapsing between the initial vibrations of the two heart sounds (p. 175). The time from the commencement of the primary wave in the central arterial pulse (p. 153) to the bottom of the incisura will give the length of the ejection phase, i.e., the time elapsing between the opening and closing of the semilunar valves. The difference between

the time of duration of the whole of systole and that of the ejection phase will give the length of the isometric period. An estimate may also be made of the total length of ventricular systole by measuring the interval from the beginning of R in the electrocardiogram to the end of T.

Wiggers takes as the end of the systolic period not the actual moment of closure of the semilunar valves but the point where the intraventricular

Duration of different phases of ventricular systole in the human heart

		seconds
Systolic phases:		Total duration 0.15-0.26
Isometric contraction period (pre-sphygmie)		0.04-0.06
Period of ejection (sphygmie)		0.21-0.30
Maximum ejection		0.09-0.14
Reduced ejection		0.12-0.16



FIG. 66. Scheme summarizing consecutive phases of cardiac cycle (after Wiggers).

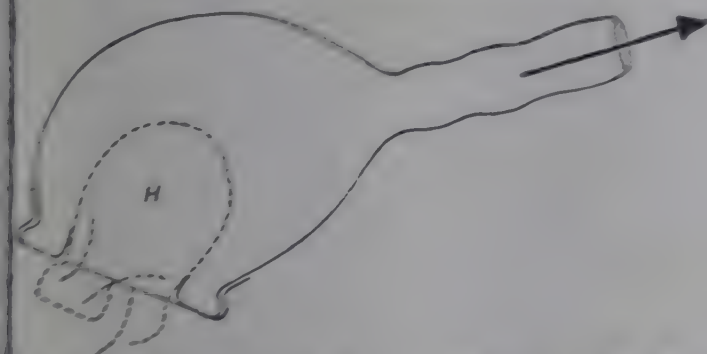


FIG. 67. Henderson's glass cardiometer. H., heart. Arrow is directed towards recording apparatus.

pressure drops suddenly to produce the incisura (p. 153). He further divides the ejection period into two phases. The first of these is termed the period of *maximum ejection* (from line 2 to line 3 in figure 66), which extends from the opening of the semilunar valves to the point of maximal pressure. The somewhat longer second phase during which the pressure is declining gradually and the outflow is lessening is termed the period of *reduced ejection* (line 3 to line 4). The interval elapsing between the end of the latter period and the closure of the semilunar valves, i.e., while the incisura of the central arterial pulse is being inscribed (line 4 to line 5), is included by Wiggers in the diastolic period and termed the *protodiastolic phase*. In the dog's heart the total duration of systole as thus defined was found to be from 0.15 to 0.26 second. The periods of maximum and reduced ejection were 0.05 to 0.12 and 0.06 to 0.14 second respectively.

The phases of ventricular diastole

The postsphygmie period or period of isometric relaxation and the protodiastolic phase of Wiggers have already been mentioned. After the opening of the A-V valves (at the end of the period of isometric relaxation) the blood flows rapidly into the ventricle; the intraventricular pressure curve falls to the zero line (line 6 to line 7 fig. 64). This is spoken of as the period of *rapid filling*. Unless the heart is beating rapidly the period of rapid filling is followed by one during which the ventricle, being already nearly full, fills more slowly. During this period (line 7 to line 8) the ventricular volume increases very little; the intraventricular pressure may rise slightly. The term *diastasis* has been given to this phase by Henderson. Auricular systole follows the period of diastasis and, as already seen, causes the small pressure wave in the ventricular curve at the end of the diastolic period. It has been pointed out (p. 170) that only the first half of auricular systole is responsible for this pressure rise. The period of diastasis is much curtailed or abolished when the heart beats rapidly, in which event auricular systole may ensue at the end of the phase of rapid filling, or after only a brief period of diastasis. The period of diastasis lengthens of course as the heart rate slows. The phases of the cardiac cycle are shown diagrammatically in figures 65 and 66.

Duration of different phases of diastole in the human heart

Diastolic phases:	Total duration	seconds
		averages
	0.50	
Protodiastolic period (Wiggers).....	0.04	
Isometric relaxation (post-sphygmie).....	0.08	
Rapid inflow.....	0.09	
Diastasis	0.19	
Auricular systole	0.10	

The volume curve of the ventricle

By enclosing the ventricles in a chamber as shown in figure 67 and connecting the cavity of the chamber to a recording apparatus the changes in volume of the heart during the cardiac cycle may be studied. Such an instrument is called a *cardiometer*. The curve so obtained is of course quite different from the intraventricular pressure curve (see fig. 64).

CHAPTER XXII

THE MOVEMENTS OF THE HEART VALVES. THE HEART SOUNDS

The chief factor concerned in the opening and closing of the valves is, as already indicated (p. 171) the difference in pressure upon their opposite surfaces. Some additional features of the valvular mechanisms must now be considered.

THE AURICULO-VENTRICULAR VALVES (TRICUSPID AND MITRAL)

The valve leaflets or cusps, three in number on the right and two on the left side, are attached by their bases to the fibrous rings surrounding the auriculo-ventricular openings. Their free margins are connected through delicate tendons (chordae tendineae) to the papillary muscles which prevent inversion of the valves into the auricle during ventricular systole. The chordae tendineae are tightened at the commencement of systole by the contraction of the papillary muscles. The leaflets are composed mainly of a double layer of the endothelial lining of the heart, strengthened by a few connective tissue fibers. Their attached bases are thicker and contain more connective tissue, small blood vessels and delicate strands of smooth muscle. The latter, however, play no part in valve closure which is effected, as mentioned above in a passive manner.

The mechanism of valve closure

During auricular systole the leaflets do not lie back against the ventricular wall, but occupy a mid-position as a result of two opposing currents. The inflowing blood pressing upon their auricular surfaces keeps them open, while eddies reflected in the reverse direction from the ventricular walls strike their ventricular surfaces and tend to close them. Thus they float in a position of delicate balance. When, as a result of the fall in intra-auricular pressure as auricular systole terminates, the incoming jet is diminished in force and finally ceases, the back eddies persisting for a brief space and being unopposed, approximate the valves or bring them gently into apposition (fig. 68). They are not, however, firmly closed. This is effected by the rise in pressure in the ventricle when it contracts. Dean has shown by attaching a hair to the septal leaf of the valve and recording its movements, that if ventricular systole does not

follow almost instantly upon the cessation of the flow of blood from the auricle the valves start to reopen. In instances, therefore, in which ventricular systole is delayed, that is, when the A-V interval is prolonged, the reopening of the valves proceeds for an appreciable time. Then, when ventricular contraction occurs a small amount of blood regurgitates into the auricle before the valves are swung closed by the rising intraventricular pressure. The backward flow of blood through the orifice may then give rise to a murmur just preceding the first heart sound (presystolic murmur).

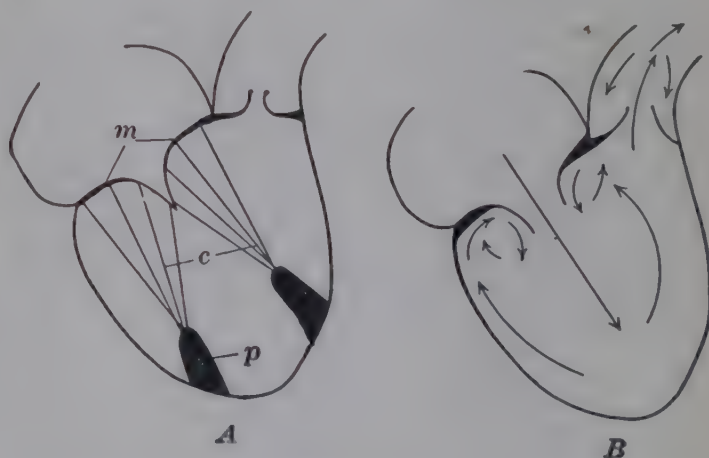


FIG. 68. Two diagrams showing mechanisms concerned in valve closure. A, showing relations of papillary muscles and chordae tendineae to valve flaps; B, partial closure due to eddy formation (after Wiggers).

THE SEMILUNAR VALVES

The dynamics of aortic and pulmonary closure are essentially the same in principle as those described for the A-V valves. The valves form three small pockets open toward the arterial lumen. Back eddies which are set up during the ejection phase of systole prevent the contact of the valves with the arterial wall. When ejection ceases the centripetal currents carry the valves into apposition and firm closure is effected by the higher pressure upon their arterial surfaces at this time.

THE HEART SOUNDS

Two sounds can be heard during the cardiac cycle. The *first sound* is of relatively long duration, soft in quality and low in pitch. The *second sound* is shorter, sharper and of higher pitch.

These characteristics are best imitated vocally by the syllables "lub" and "dup" separated by a brief pause. The two heart sounds mark the beginning and end of ventricular systole and the determination of the interval between their commencements (as determined by the phonocardiogram) is the most reliable method for arriving at the length of ventricular systole in man. The pause between the end of the second sound and the beginning of the first coincides with ventricular diastole.

The factors concerned in the production of the sounds

THE FIRST SOUND is heard most clearly and at maximal intensity by placing a stethoscope over the fifth left intercostal space ("apex beat"). It is generally taught that two factors, at least, enter into the production of the first sound, (1) contraction of the ventricular muscle and (2) the closure of the A-V valves and the vibration set up by the tension of the valve leaflets and chordae tendineae as the intraventricular pressure rises.

The contribution which other events make to the production of the first heart sound, e.g., the opening of the pulmonary and aortic valves, the rush of blood from the ventricles and the shock transmitted to the walls of the pulmonary artery and aorta, have been the subject of much debate but there is no general agreement. Some deny that the sound is prolonged into the period of ejection and, therefore, would exclude these factors from participation in its production. The observations of Straub and of Orias and Braun-Menendez indicate that the sound is prolonged beyond the isometric period, and it is probable that some, if not all, of the factors mentioned play a part, if only a minor one, in producing it. There is no doubt that the vibrations set up in the leaflets of the auricular-ventricular valves as they are put under tension at the beginning of ventricular systole, constitute an important factor in the production of this sound. The existence of a muscular element, however, has been questioned. Dock recorded the sound vibrations by means of a phonocardiograph applied to the surface of the heart and reported that no sound was produced when the empty heart contracted, valve action being abolished. Although he concluded from this that the normal first sound contained no muscular element, evidence from other sources is strongly opposed to such a conception. Wiggers and Dean, previously, had recorded sound vibrations from an isolated strip of myocardium. It has also been shown that when free movement of the

valves of the beating heart is prevented, the booming character of the first sound still persists.

Phonocardiographic records from the chest over the heart show no vibrations before the onset of ventricular contraction (fig. 64) thus indicating that the presystolic apposition of the valves is silent. The sound commences 0.008 second before the peak of the R wave of the electrocardiogram. Its duration is about 0.18 second.

THE SECOND SOUND results from the vibrations set up in the blood column and arterial walls, as the aortic and pulmonary valves are placed under tension following their closure. The duration of the second sound is about 0.10 second. It commences about 0.09 second after the summit of the T wave of the electrocardiogram. It is heard best over the pulmonary and aortic areas—the upper part of the sternum adjacent to the second left intercostal space, and the second right costosternal junction, respectively.

THE THIRD HEART SOUND. Sometimes a faint third sound is heard in normal hearts which follows the second sound by about 0.08 second and lasts for about 0.04 second. It is heard at the apex and is commonly found in young adults. Thayer found it present in 65 per cent of normal individuals. It may be made to appear or is intensified by procedures which increase the venous flow into the auricles, e.g., exercise, recumbent position, etc. The sound was first described by Gibson and independently by Herschfelder; several explanations have since been given to account for it. (1) Some have considered it to be due to the asynchronous closure of the aortic and semilunar valves, but the interval between it and the second sound is too great for the acceptance of this explanation. (2) White considers that it is due most probably to the opening snap of the A-V valves or to the vibration of the ventricular walls as the blood rushes into the ventricle. (3) Another view is that the sound is simply due to prolonged after vibrations of the aortic valves which have become separated from the earlier vibrations as a silent interval. None of these explanations is entirely satisfactory in all instances.

Variations in the intensity of the heart sounds

It is the general belief that the first sound varies in intensity with the force of ventricular systole and the loudness of the second sound with the height of the arterial blood pressure. The experiments of Wiggers bear this out. The sounds were recorded graphically and correlated with the intraventricular and aortic pressure curves. It was found that the vibrations of the first sound were increased in amplitude and number when the

tension developed by the cardiac muscle was increased. The intensity of the first sound is directly related to the rate of the pressure rise within the ventricle during the isometric period. The intensity of this sound is not dependent upon the volume of the systolic discharge but rather upon the diastolic pressures in the pulmonary and systemic circuits. Wiggers found that when the heart was slowed and the systolic discharge consequently increased but the diastolic pressure lowered, the intensity of the first heart sound was reduced while acceleration of the heart (reduced

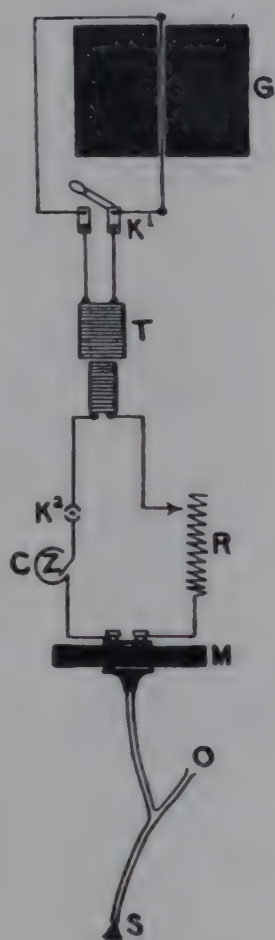


FIG. 69. *S*, stethoscope bell; *O*, side tube to air; *M*, microphone; *C.Z.*, dry cell; *R*, resistance; *K¹*, key in galvanometer circuit; *T*, induction coil; *K²*, key in microphone circuit; *G*, galvanometer (after Lewis).

systolic discharge with raised diastolic pressure) increased its intensity.

The intensity of the second sound in the aortic or pulmonary area is increased by an elevation in the systemic or pulmonary pressures, respectively. Among the cardiovascular conditions associated with intensification of the second sound are, mitral stenosis and failure of the left ventricle which raise the pulmonary arterial pressure, and arterial hypertension which raises the aortic pressure.

THE GRAPHIC REGISTRATION OF THE HEART SOUNDS.
The phonocardiogram. The instrument employed for this purpose consists of a stethoscope fastened to the

chest and provided with a side-tube open to the air so as to obviate pressure changes, a microphone and a string galvanometer (fig. 69). A type of apparatus devised more recently (Kauntz and associates) avoids the acoustic errors of air transmission and employs a water-filled capsule in contact with the chest. The vibrations are picked up by a dynamic type of microphone. The electrical currents are transmitted to an amplifier and thence to the vertical plates of two cathode tubes. The vibrations are recorded photographically.

The record of the first sound is composed chiefly of a series of from 7 to 13 vibrations. These are of small amplitude to start with but rise to a "crescendo" which reaches its maximum at the end of the isometric period and is followed by a "diminuendo" of about the same duration. This main series of vibrations is preceded by a couple of small introductory vibrations which occur prior to the ventricular pressure rise. These are possibly of auricular origin. The main series is also followed by a few final vibrations, variable in number. The vibrations are in general irregular, which places the sounds in the category of noises rather than of musical tones. The frequency is low, being on the average 45, 50, and 33 per second, respectively, for the first, second and third sounds. A normal and a series of abnormal phonocardiograms are shown in figure 70, page 178.

Graphic registration of the heart sounds has permitted precise relationships to be established between them and the events of the cardiac cycle, as recorded by other graphic methods, e.g., intracardiac pressure curves and the electrocardiogram. The phonocardiogram also, as already mentioned, provides an accurate method of measuring the length of ventricular systole.

ABNORMAL HEART SOUNDS

Murmurs

When the valves at one or other of the cardiac orifices become deformed by disease, they impede the flow of blood or allow leakage to occur, and abnormal sounds replace either partially or completely the usual heart sounds. Such sounds are spoken of as murmurs or bruits. When the valves produce narrowing of one of the orifices of the heart, the condition is spoken of as *stenosis*; thus *aortic* or *mitral stenosis* implies restriction of the respective opening and increased resistance to the flow of blood through it. The velocity of the blood flow through the constricted orifice is also increased. The valve surfaces are usually roughened and the smoothly rounded and somewhat funnel-shaped nature of the opening is lost. All these factors contribute toward the abnormal sound. When the valves are incapable of closing tightly they are said to be *incompetent*. They no longer perform their duty but allow blood to pass through

the orifice in a direction the reverse of that of the circulation. So *aortic* or *mitral incompetence* or *regurgitation* is spoken of to indicate leakage of the respective valve. Obviously if the valves are deformed sufficiently to produce narrowing of a particular orifice, they will also be incapable of closing properly and leakage will occur as well.

of blood at this time. At the end of the period of ejection they should close tightly. If however the orifice is stenosed, the obstruction causes a murmur to be heard during ventricular systole which replaces or modifies the clear first sound. This is referred to as a *systolic murmur*. If, on the other hand, the valves are incompetent and do not come together at the end of the

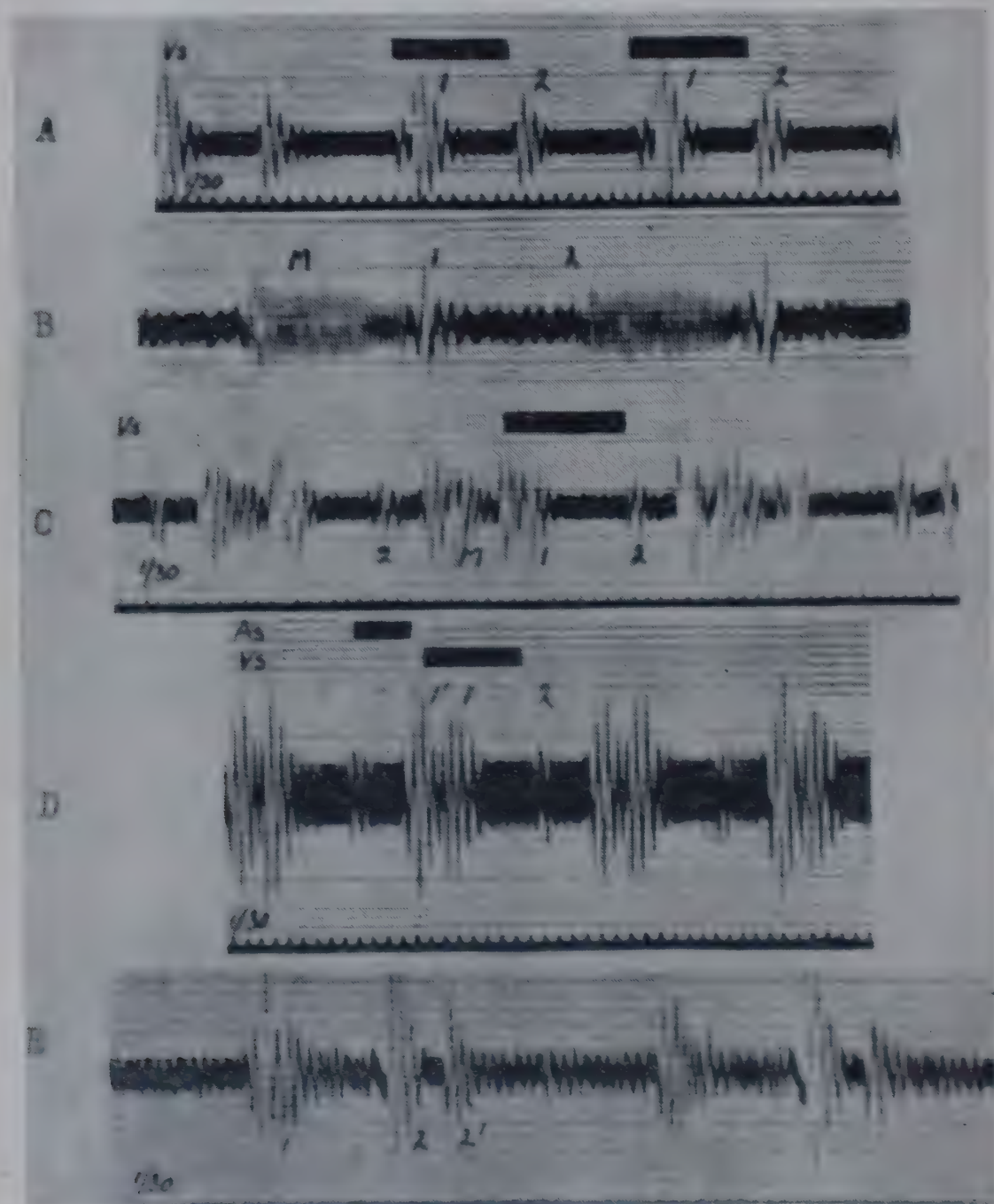


FIG. 70. A, normal heart sounds recorded from apex; B, a diastolic murmur of aortic origin; C, presystolic murmur; D, gallop rhythm, presystolic (1') type; E, gallop rhythm, early diastolic (2') type. The numbers 1 and 2 refer to the heart sounds; M, murmur (after Lewis).

Stenosis is therefore usually associated with a certain degree of incompetence.

TIME RELATIONS. The particular valve involved is determined from the relation of the murmur to the events of the cardiac cycle and from the point upon the chest wall where the sound is transmitted with the greatest intensity. For instance, the aortic valves should be open during the ejection phase of ventricular systole so as to offer little or no resistance to the outflow

systolic discharge, a rush of blood from the aorta into the ventricle occurs in diastole, and a murmur modifies the normal second sound—*diastolic murmur* (fig. 70 B). The murmur may appear in early, mid-, or late diastole or may persist throughout almost the entire period. When stenosis and incompetence co-exist a murmur may be produced at the aortic orifice during both systole and diastole, in which event the two normal sounds are replaced by a to and fro blowing sound. A systolic murmur will also be caused by incompetence of the

A-V valves (tricuspid or mitral) since the rise in pressure during ventricular systole will drive blood backwards into the auricle and cause abnormal vibrations to be set up.

Mitral stenosis (stenosis of the tricuspid orifice is very rare) by offering an obstruction to the flow of blood from the auricle into the ventricle may cause a murmur to be heard at any time between the second and the first heart sounds. The intensity, duration and timing of the sound vary with the degree of stenosis and the rate of blood flow through the orifice. Though the murmur may extend throughout diastole it tends to be more intense toward the beginning and the end of diastole; it may be heard only during these times, or be confined to one or other of them. As pointed out by Lewis, the rate of blood flow into the ventricle which is an important factor in the production of the abnormal sound, is most rapid during these phases of diastole. At the end of diastole an impetus is given to the blood by the systole of the auricle; while the early part of diastole is the period of rapid filling (p. 173) of the ventricle. The late diastolic murmur (presystolic) may therefore disappear when auricular fibrillation supervenes and abolishes the propulsive action of auricular systole. When the heart is beating slowly the murmur is more likely to be well marked in early and in late diastole. The blood which has accumulated in the auricle during the preceding ventricular systole rushes through the mitral orifice when the valves open, but the flow slows as the ventricle becomes full (period of diastasis), so the murmur disappears. It reappears again when the auricle, distended with blood as a result of the prolongation of diastole, contracts. When the beat is rapid and the period of diastasis abolished, the murmur is likely to be heard throughout diastole which is then occupied entirely by the phase of rapid filling. Aortic regurgitation is not uncommonly associated with a presystolic murmur. Such as described many years ago by Austin Flint and is usually referred to as the *Flint murmur*. According to the most generally accepted explanation, it is due to vibrations set up in the anterior leaflet of the mitral valve which is pushed by blood regurgitating through the aortic orifice into the path of the stream entering from the auricle. Gouley has described a characteristic deformity of the right leaflet of the aortic

valve which he declares served to direct the regurgitating blood against the mitral leaflet.

GALLOP OR CANTER RHYTHMS. In certain cardiac conditions three distinct sounds are heard which give rise to a rhythm not unlike the gallop or canter of a horse. In some cases the abnormal sound precedes the first sound—the *presystolic type* of gallop rhythm. Two sounds are heard in rapid succession followed by a pause, and then by the second sound (fig. 70, D). This type is associated with depressed auriculo-ventricular conduction (p. 190) or sometimes with bundle branch block (p. 192). The extra sound is attributed to the forceful contraction of the auricle. Ordinarily the ventricular contraction follows so closely upon auricular systole that any sound set up by the contraction of the auricle merges with the first sound. But when, as a result of slowed conduction in the A-V bundle, the auricular and ventricular systoles are separated by an appreciable interval the contraction of the auricular muscle may become audible. The engorgement of the auricle, due to the delay in the ventricular contraction and the hypertrophy of the auricular muscle which frequently exists, also favor the production of the sound.

In other cases the abnormal sound follows shortly upon the second heart sound—*early diastolic type* of gallop rhythm (fig. 70, E). In some instances the extra sound is simply an intensification of the third sound described above as occurring in normal subjects. It may then, though very occasionally, follow strenuous muscular exercise. In most instances this type of gallop rhythm is associated with cardiac failure and is then indicative, usually, of a severe myocardial damage. The abnormal sound is not caused by asynchronous closure of the pulmonary and aortic valves. It is most probably due to vibrations set up in the walls of the dilated ventricle caused by the shock of blood as it rushes from the auricle under a high head of pressure. The sound therefore follows upon the opening of the A-V valves, i.e., after the period of isometric relaxation (p. 173).

When the heart rate is slow and auriculo-ventricular conduction much prolonged, a type of gallop rhythm may develop in which the abnormal sound occurs near the middle of diastole—*mid-diastolic type* of gallop rhythm—and is attributed to a forceful contraction of the auricle.

CHAPTER XXIII

ELECTROCARDIOGRAPHY. THE VENOUS PULSE

GENERAL DESCRIPTION OF THE ELECTROCARDIOGRAPH

The electrocardiograph as devised by Einthoven is, in essence, a very sensitive galvanometer. The cardiac action current is led through a fiber of finely spun silver-coated quartz glass, 0.002 mm. in diameter (about $\frac{1}{4}$ of the diameter of a red cell). The fiber, or "string" as it is termed, is suspended vertically in a holder between the poles of an electromagnet. When the magnet is excited by a powerful current an electric field is set up, the lines of force passing from its north to its south pole. The heart current is conducted through the string (fig. 71). A strong beam of light is directed through apertures in the arms of the magnet lying in front of and behind the string. The latter and its lateral movements (deflections) are thus cast as shadows which are magnified and brought to a focus upon a moving photographic surface (plate, film or sensitive paper) moving vertically at the desired speed in a camera of special design.

The sensitivity of the string is standardized so that a deflection of 1 centimeter represents 1 millivolt. Horizontal lines a millimeter apart are marked on the record by means of etchings upon the camera lens. Each division represents $\frac{1}{10}$ millivolt. The shadows thus cast upon the photographic surface are registered as the deflections or waves in the electrocardiogram mentioned above and described in detail on page 181.

The passage of the heart current causes circular lines of force to be set up around the fiber. These take a clockwise or anti-clockwise direction according to the direction (descending or ascending) taken by the cardiac current, and cause the string to move, respectively, inwards toward the arch of the magnet or outwards. Time is indicated by vertical lines caused by some form of timing device which breaks the beam of light at regular intervals. The finer vertical lines indicate $\frac{1}{8}$ second, heavier ones $\frac{1}{4}$ second.

The string galvanometer type of electrocardiograph is the one in most general use today but within recent years an instrument employing a moving magnet or moving coil galvanometer and radio tube amplification has been devised.

THE ELECTROCARDIOGRAPH LEADS

We have already seen (p. 165) that the electromotive force developed in the cardiac muscle of an

experimental animal can be recorded by placing paired contacts directly upon the surface of the heart and connecting them with a galvanometer or by placing one contact upon the heart and the other upon some indifferent part of the body. Records obtained in this way are called *electrograms*. It is clear that the electrical changes occurring immediately beneath a contact electrode will dominate the record. The heart *in situ* is, however, surrounded by a conducting medium—the blood and tissue fluids which are, in fact, solutions of electrolytes. It is possible, therefore, to connect the electric field set up about the heart during its beat by leading off from certain paired regions upon the body surface to the string of the electrocardiograph. A part of the electromotive force developed by the heart can in this way be "tapped" and the activity of any part of the cardiac muscle, and not merely the region beneath the electrodes as in the case of electrograms, will impress its influence upon the electrocardiogram. The parts of the body employed for this purpose are the two forearms (or hands) and the left leg (or foot). These may be coupled in any one of three combinations, each of which is referred to as a *lead*. Thus the three standard leads are—

Right arm and left arm = *lead I*

Right arm and left leg = *lead II*

Left arm and left leg = *lead III*

Flat pliable metal electrodes (3" x 2" in area) covered with gauze soaked in strong salt solution or with a jelly composed of salt, tragacanth, glycerine and water are applied to the forearms and the left leg above the ankle. By means of a switch on the control board of the electrocardiograph, a record from each lead can be taken in turn.

A fourth or precordial lead is now frequently used in addition to the three standard leads and is generally recommended as a routine procedure. Wolferth and Wood showed that if only the three standard leads were used, important electrocardiographic changes occurring in the antero-posterior diameter may be missed. For recording the precordial lead, one electrode is placed upon the fourth intercostal space to the left of the sternum, the other on the posterior wall of the chest directly opposite the first. The anterior electrode is attached to the right hand terminal of the control box and the posterior electrode to

the terminal for the left hand. The P wave in lead IV is frequently inverted or notched and may be diphasic. The P-R interval is longer by from 0.01 to 0.03 second than in lead II. The R wave is, as a rule, higher (20 mm. or more) than in the standard leads, the Q wave is very pronounced and the S wave absent. The T wave is usually inverted.

THE NORMAL ELECTROCARDIOGRAM

During the cardiac cycle the electrical changes in the heart cause five distinct movements or deflections of the galvanometer string. Three of these are directed inward, i.e., toward the arch of the magnet; two are directed outward. The photographic surface, as we have seen, moves

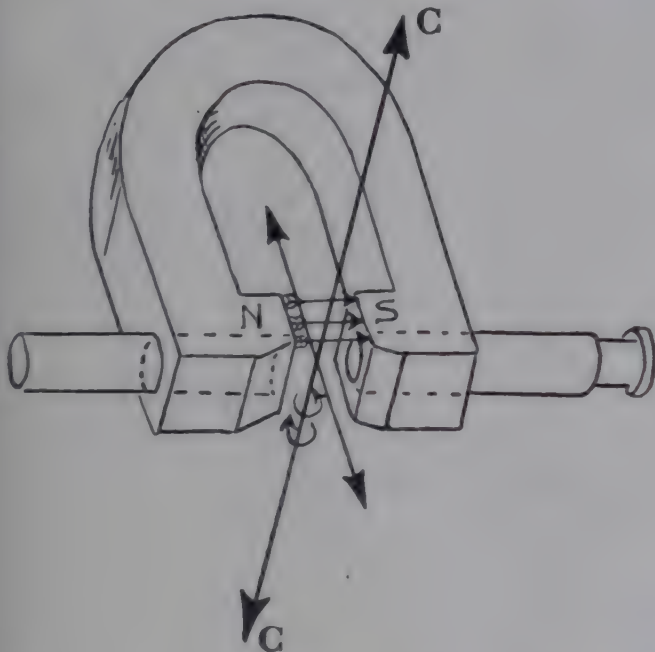


FIG. 71. C, C, galvanometer string; N and S, north and south poles of electromagnet. Further description in text.

perpendicularly from above downward. The movements are, in consequence, marked in the record as deflections to one or other side of a vertical zero line representing the isoelectric position of the string. The electrocardiogram, however, is always examined after rotating the plate to the left into the horizontal position, when the deflections appear as waves above or below the zero line. The waves from left to right have been designated simply by the letters of the alphabet, P, Q, R, S and T (fig. 72). P, R and T are directed upward, Q and S downward. Q is not always present. A fourth small positive wave, U, is sometimes seen in leads I and II immediately following T. Its significance is unknown. The ventricular lines in this figure mark fifths of seconds; the horizontal lines, 1 mm. apart, indicate tenths of millivolts.

The P wave is produced by the spread of the excitation wave over the auricles. Notching of the P wave not infrequently occurs in leads II and III, and occasionally in lead I. The duration of the P deflection as measured along the base line averages 0.08 second. It precedes the auricular contraction by about 0.02 second.

The Q, R, S and T deflections are produced by the ventricles, the first three waves during the spread, and the T wave during the retreat of the excitation wave (p. 187). The duration of the QRS complex varies inversely with the heart rate (usually from 0.04 to 0.08 second). A duration exceeding a tenth of a second is abnormal.

The R wave commences about 0.02 second before the beginning of the rise in the intraventricular pressure curve (p. 171); it reaches the base line again before the semilunar valves open.

The duration of the P-R interval (from the beginning of P to the beginning of QRS) varies inversely with the heart rate; the normal range being from 0.15 to 0.20 second in lead II. It is somewhat shorter in the other standard leads and longest in lead IV. The length of the interval is taken as an index of the conduction time over the auriculo-ventricular connections. A value exceeding the upper normal limit of a fifth of a second (with heart rate of 70 or over) indicates an abnormally slow conduction rate (p. 190).

The S-T interval, that is, the interval elapsing between the end of the S wave and the commencement of T during which the record closely follows the base line, varies in length from 0.10 to 0.25 second according to the rate of the heart. It coincides approximately with the period of maximum ejection of ventricular systole (p. 172). The end of the T wave corresponds in time with the beginning of the period of isometric relaxation, i.e., to the closure of the semilunar valves. A measurement of the Q-T interval (beginning of Q to end of T) gives the length of ventricular systole. The Q-E interval, i.e., the lapse of time between the commencement of the Q wave and the commencement of ventricular ejection as determined from the subclavian pulse, is from 0.10 to 0.16 second.

Voltages. The highest wave of the electrocardiogram (R wave) in lead II varies in amplitude among normal subjects from 7 to 18 mm. (i.e., potential values of from 0.70 to 1.80 millivolts). The relative heights of the other deflections may be seen in figure 72.

THEORY OF ELECTROCARDIOGRAPHIC INTERPRETATION

EINTHOVEN'S TRIANGLE

First let a geometrical proposition be considered. Let an equilateral triangle, ABC, be described and a straight line, DE, be drawn in any direction within it,

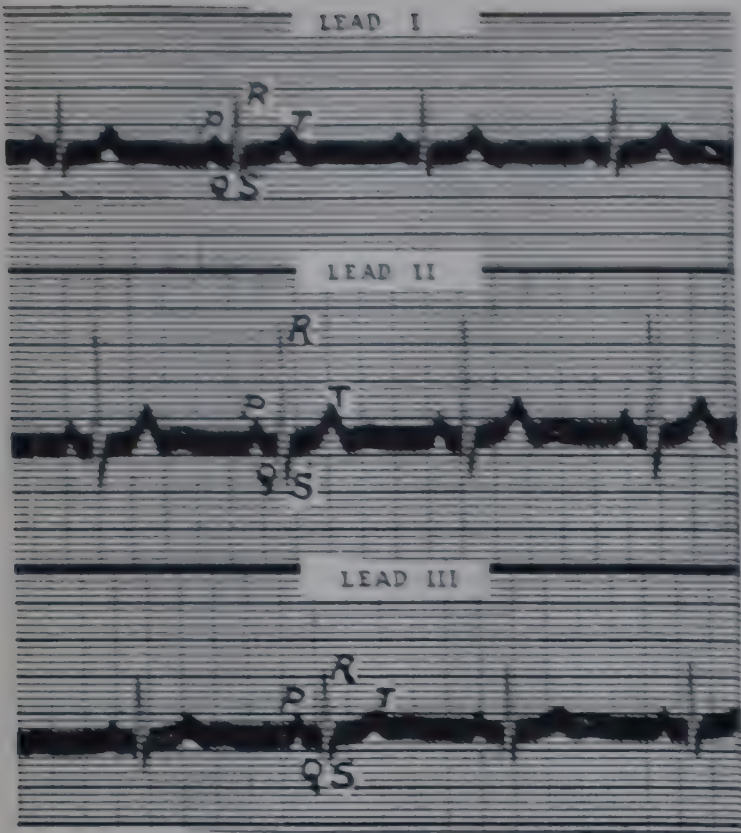


FIG. 72. Normal electrocardiogram (kindness of Dr. John Hepburn).

and let this line be projected perpendicularly on to the three sides (P_1 , P_2 and P_3 , fig. 73, I). Then the longest projection (which in the illustration is P_1) equals the sum of the other two (i.e., P_1 and P_2 in the instance depicted. This is true no matter what may be the direction of DE.

Next let a plate of conducting material be fashioned in the form of an equilateral triangle (fig. 73, II) and let any two apices of the triangle be connected through a galvanometer so that when the fall in potential is from A to C either through B or directly to C the galvanometer deflection is upward, i.e., positive, and when the fall in potential is in the opposite direction, the deflection is downward or negative. When an electromotive force, whose magnitude and direction are represented by one or other of the two central arrows shown in the figure, is developed within the triangle, then the potential difference between any two of the latter's apices will be proportional to the length of the projection of the arrow upon the side connecting these apices. The length of the projection on a given side of the triangle, and so the recorded potential change which it represents, will vary, of course, with the angle which the arrow makes with that side. Whether the central EMF produces an upward or a downward deflection will de-

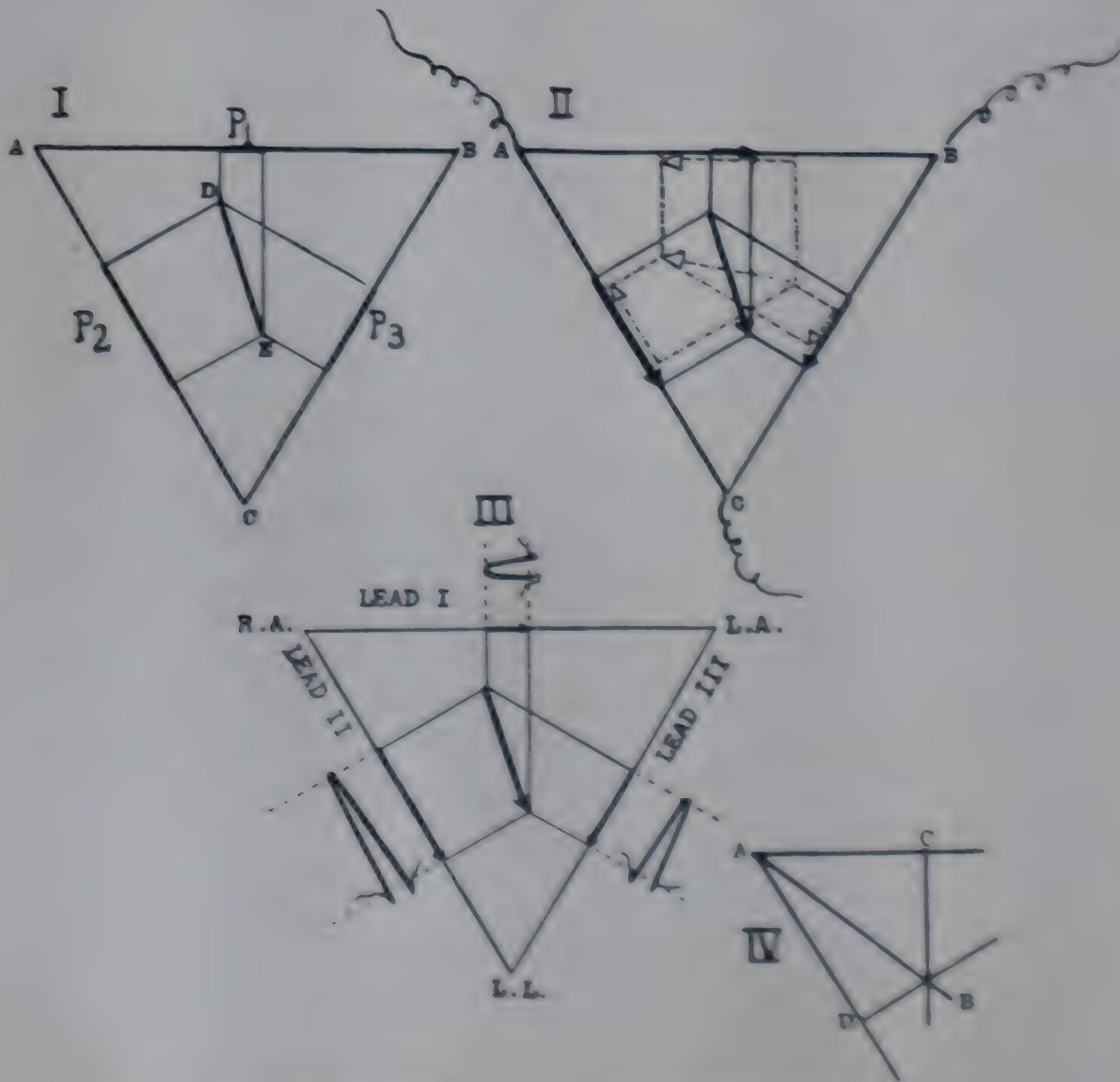


FIG. 73. Description in text. Vertical lines mark $\frac{1}{2}$ sec.

and upon its general direction. In the figure all the projections of the solid arrow are positive; two of the projections of the arrow drawn in interrupted lines are negative and one positive. But the arrow might point in any direction, and depending upon its direction in relation to a given side of the triangle its projection upon that side will be of positive or of negative sign. It will be found, nevertheless, that in whatever direction the arrow points, the *algebraic* sum of its projections on the sides AB and BC will equal its projection on AC. Finally, let the three electrocardiographic leads be imagined as forming an equilateral triangle about the heart (fig. 73, III); let the electrical axis of the heart (p. 184) be represented by the arrow, and the potential differences, negative or positive, which are recorded (as deflections) in the electrocardiogram in the three leads, be taken to correspond to the projections of the arrow upon the respective sides of the triangle. Then the potential difference between any two points upon the body represented by the apices of the triangle will vary in magnitude according to the angle which the arrow makes with the lead joining these points, and be proportional to the projection of the arrow upon the line of the lead. So the *algebraic sum of the potential differences as recorded in leads I and III will equal that recorded in lead II*. This truth, first enunciated by Einthoven, is expressed by the following formula, $e^1 + e^3 = e^2$, in which e represents potential difference and the numerals the respective leads. It forms the basis for the interpretation of the electrocardiogram. It is a remarkable fact that such a mathematical formula, though empirical as applied to electrocardiography, is in such close agreement with the actual facts derived from experiment.

THEORY OF LIMITED POTENTIAL DIFFERENCES

It has been supposed that the excitation wave travelled through ventricular muscle from the base (region of A-V ring) to the apex of the heart and then from apex to base, and so followed a course laid down by the doubling upon itself of the embryonic cardiac tube (notch). The excitation wave commencing at the base caused, it was supposed, this region to become negative to the apex, and so produced a deflection upon the line of the tracing, i.e., the R wave. The wave on moment later having reached the apex caused this to become relatively negative, the current was reversed and a deflection—the S wave—was inscribed below the zero line. The return of the wave to the base in the region of the great vessels and its final retreat from this part is believed to cause the T wave.

But this simple explanation is no longer satisfactory. The excitation wave does not spread through the ventricular muscle in this manner. As we have seen, the wave follows a more or less semicircular course around the interior of each ventricle along the branches of the bundle and the Purkinje network. The rate of travel is very rapid, the wave taking only about 0.04 second to complete its journey. Also, it moves in a different

direction in each ventricle—clockwise in the right, and anti-clockwise in the left—exciting in its passage the overlying muscle (fig. 75). Thus regions quite local in nature and perhaps within a single muscle fiber itself are created, which are relatively negative to the unexcited tissue which immediately adjoins and precedes them. So are visualized paired electrical charges of opposite sign but of equal value. These, which may be likened to minute batteries each with its positive (active tissue) and negative (inactive tissue) poles, are referred to by Craib as *electrical doublets*. The rest of the heart is electrically neutral at the moment and not concerned with the development of potential differences. As the excitation process spreads through the Purkinje

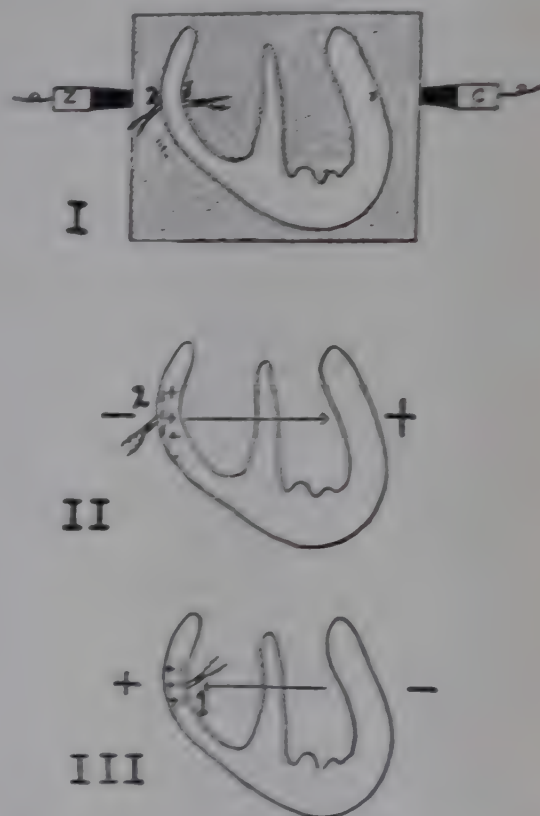


FIG. 74. Illustrating the evidence provided by an experiment of Lewis' for the theory of limited potential differences, see text (after Lewis).

system, muscle fibers in each ventricle become successively involved with the production of innumerable action currents which flow outward through the muscle.

The heart muscle then must be looked upon electrically, not as a whole, i.e., a mass of muscle over which the electrical change spreads in a regular manner from base to apex and subsequently from apex to base, but rather as consisting of innumerable units in which action currents having different directions at any given instant and from one instant to the next, are developed. Some of these will neutralize, others will reinforce, one another. It is the algebraic sum of these potential changes which determines the potential differences as recorded by the electrocardiograph. The resultant of the electromotive forces developed within the heart at any instant will have a certain definite direction which is spoken of as the *electrical axis of the heart*. It is the direction of current flow, i.e., of the electrical axis rather

than the location relative to one another of two oppositely charged masses of cardiac muscle, which determines the characters of the electrocardiogram. The foregoing view of the electrical changes is known as the theory of *limited potential differences*. The theory of *distributed potential differences*, as the base to apex view is termed, has been shown inapplicable by the following experiment of Lewis.

In figure 74, I is represented a heart immersed in saline. The electrodes Z and C are connected through a galvanometer. If, as shown in figure 74, II, the epicardial surface be stimulated at 2, a region of negativity is created, the electrode Z becomes negative to electrode C, and a current flows as indicated by the arrow. The duration of flow might be explained by either theory, for it is seen that whether the tissue Z is relatively negative to the rest of the entire ventricular muscle, as the theory of distributed potential differences demands, or is negative only to a region immediately adjoining itself, the current's direction will be the same. If, however, the endocardial surface is stimulated at 1, fig. 74, III), then the current first flows in the opposite direction; Z is positive and C negative. This is incompatible with the older theory since, if the point of stimulation is relatively negative to all unexcited regions of the heart, the current should be in the same direction as when the epicardial surface was stimulated. It has also been shown that the S wave is actually produced by the spread of the excitation wave to the region of the base, and not by the development of negativity at the apex, which alone could satisfy the base to apex theory. Furthermore, in the cold-blooded heart the base is not always activated before the apex, yet an upright R wave is found in any event.

THE ELECTRICAL AXIS OF THE HEART

Determination of the electrical axis

The graphic method of Fahr may be employed. In order to determine the direction for the electrical axis records are taken in leads I and II. The amplitude of the electrocardiogram at synchronous points (e.g., the R waves) in each record is measured in millimeters (1 mm. = $\frac{1}{10}$ millivolt) and the distances laid off upon the corresponding sides of the triangle (fig. 73, IV) commencing from the angle A. Perpendiculars are dropped from the ends of these measurements (C and D) toward the center of the triangle until they intersect at B. A line joining A and B gives the direction of the electrical axis at the moment that the particular deflections were inscribed. The full potential difference developed in the heart can never be known. The *manifest* value is the maximal potential difference which can be recorded, i.e., when the electrical axis lies parallel to the lead (see below). The length of AB in millimeters gives the manifest value in tenths of millivolts.

It should be pointed out that, though the electrical changes are occurring in all planes of the heart muscle, the electrocardiogram registers those in one plane only,

just as a roentgenogram depicts the heart in two and not three dimensions.

The rotation of the electrical axis

Determinations of the electrical axis at successive moments throughout the cardiac cycle have shown that its direction is continually changing. This follows naturally from the fact that the electrical axis is an expression of the balance that has been struck at the moment between separate action currents. Since the directions of these vary from instant to instant, the direction of the resultant force would be expected to vary likewise (fig. 75). During the spread of the excitation wave in the heart the electrical axis swings in an orderly manner from left to right.

The magnitude of the potential difference existing at any instant between the two electrodes of any lead depends upon the angle which the electrical axis makes with the line of that lead. This is simply expressing in another way what has been said elsewhere, that the potential difference recorded in any lead is proportional to the length of the projection of the line representing the electrical axis on to the side of the triangle corresponding to that lead. Consequently, when the electrical axis is perpendicular to the lead no potential difference is developed in that lead and the electrocardiogram, so long as the axis bears this relationship, follows the isopotential line. When the axis forms an angle greater or less than 90° with the lead, a difference of potential will be developed between its electrodes; when the axis lies parallel to a lead the maximal potential (manifest value) is established and the maximal deflection of the string occurs. Potential differences having values intermediate between zero and the maximum will be developed when the axis is other than parallel or perpendicular to the line of the lead. The magnitude of the differences will be greater or less according to the degree to which the axis swings toward one or other of these positions.

Depending upon the direction of the axis in relation to the line of the lead, the deflection may be either positive or negative. For example, if the axis is in the general direction of the small arrows shown on the sides of the lowest triangle in fig. 73, i.e., from RA to LA in the case of lead I, from RA to LL in lead II and from LA to LL in lead III, then the deflection in the respective lead will be above the base line. If the axis swings beyond the right-angle position so as to point in a reverse direction in one or other lead, then the deflection is negative in that lead.

THE COMPOSITE NATURE OF THE PHYSIOLOGICAL ELECTROCARDIOGRAM

The researches of Lewis have demonstrated that the normal electrocardiogram is in reality a record of dual effects fused together. That is, deflections are produced by electrical changes in each ventricle separately, and these become

ended together are written as the characteristic series of waves in the normal tracing. Though the excitation wave reaches both ventricles simultaneously, it spreads independently in each chamber via the corresponding bundle branch and Purkinje system (fig. 75). The direction of spread is opposite in each half of the heart, being clockwise in the right chamber and anti-clockwise in the left. If, therefore, the electrical changes could be recorded in each ventricle separately and the resultant of the action currents, i.e., the electrical axis of each ventricle, be determined, it might be expected that the axis would swing from left to right on the right side and from right to left on the left. This was found to be the case. Such experiments have shown that the electrical axis

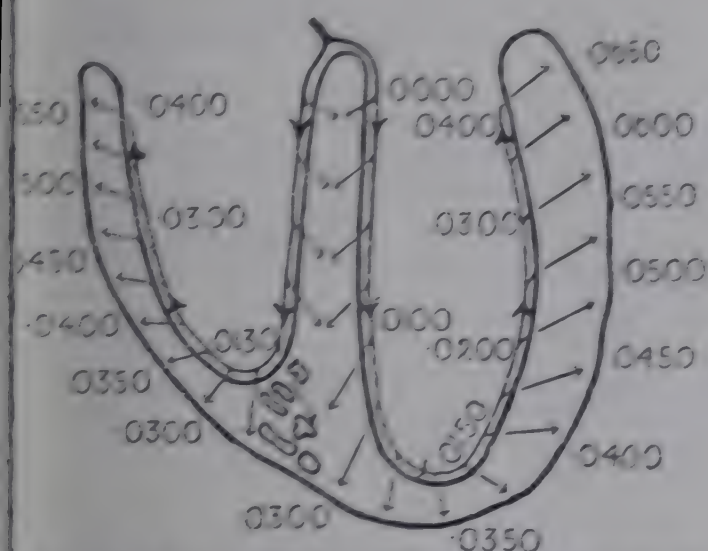


FIG. 75. A diagram of the human heart in section, presenting the directions in which the excitation wave spreads in the human ventricle and the time in seconds at which, after its commencement in the ventricle, the wave first reaches various regions of the ventricle. (After Lewis.)

of the whole heart is the resultant of the electrical axes of the two ventricles. Lewis divided (or compressed) one or other main branch of the bundle in dogs and in monkeys. When one branch of the auriculo-ventricular bundle is severed, the spread of the excitation wave to the corresponding ventricle is delayed, the electrical changes of the uninjured ventricle commence first and are consequently unbalanced by those of the opposite chamber. The QRS complex then depicts the electrical changes of the uninjured ventricle alone. When the excitation wave reaches the disabled chamber later by the only path open to it, namely, through the septum from the uninjured side and at the relatively slow conduction rate characteristic of the cardiac muscle. Lewis obtained records of the uninjured ventricle after division of the bundle of the opposite side and termed the unilateral

tracing obtained in this way a *dextrocardiogram* or a *levocardiogram* according to whether the QRS deflections represented the electrical changes in the right or left ventricle, respectively. The former was, of course, produced by left, the latter by right bundle branch injury (see fig. 77). The canine dextrocardiogram has the following characteristics. In lead I the R wave is reduced and the S wave is increased. In the levocardiogram these characteristics of the two leads are interchanged. Lead I of the levocardiogram resembles lead III of the dextrocardiogram, i.e., the chief deflection is upward. Lead III of the levocardiogram resembles lead I of the dextrocardiogram, namely, the chief deflection is downward. Extrasystoles produced by stimulation of the right or left ventricle in dogs gave records having the general features of a dextrocardiogram or of a levocardiogram, respectively (see also p. 192).

When the QRS complexes of the two sides of the heart are plotted separately on a large scale and with identical time relations (as shown for the left side in fig. 76) then a third curve can be constructed by the algebraic summation of the values in the former two. This calculated curve, termed the *bicardiogram*, presents the characteristics of the normal electrocardiogram.

DEVIATION OF THE ELECTRICAL AXIS

The direction of the electrical axis, of course, bears a relationship to the anatomical axis of the heart. The latter may be taken as passing longitudinally through the interventricular septum, being directed forward, downward and to the left and roughly parallel to the side of the triangle represented by lead II. Obviously, changes in the position of the heart in relation to the sides of the triangle enclosing it will, by causing corresponding alterations in the direction of the electrical axis, be reflected in the electrocardiogram. The heart alters its position slightly during ordinary respiration. During expiration, as a result of the ascent of the diaphragm, the apex swings upward and to the left, i.e., anti-clockwise, and the heart assumes a more transverse position; the opposite movement occurs during inspiration. Even changes in the position of the body (turning in bed from one side to the other) or distension of the stomach may cause slight changes in the direction of the anatomical axis. A rotation of the heart to the left tends to alter the direction of the electrical axis (*left axis deviation*) in such a way as to increase the amplitude of the R wave and reduce the S wave in lead I, and to reduce the

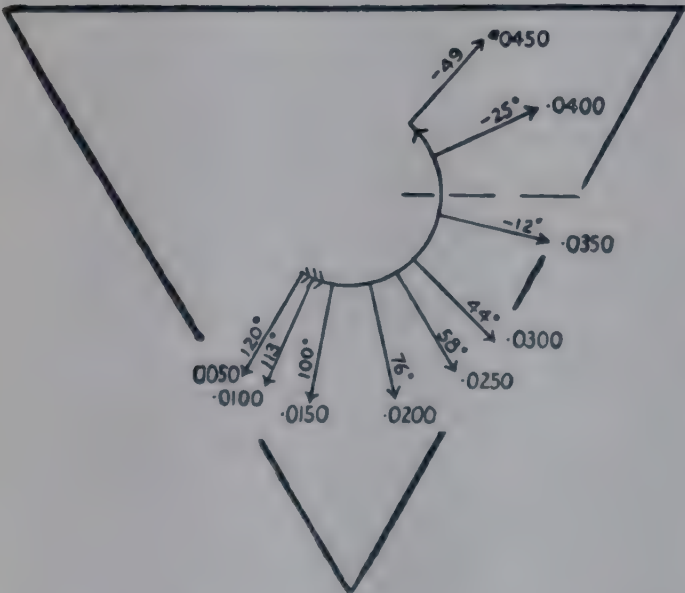
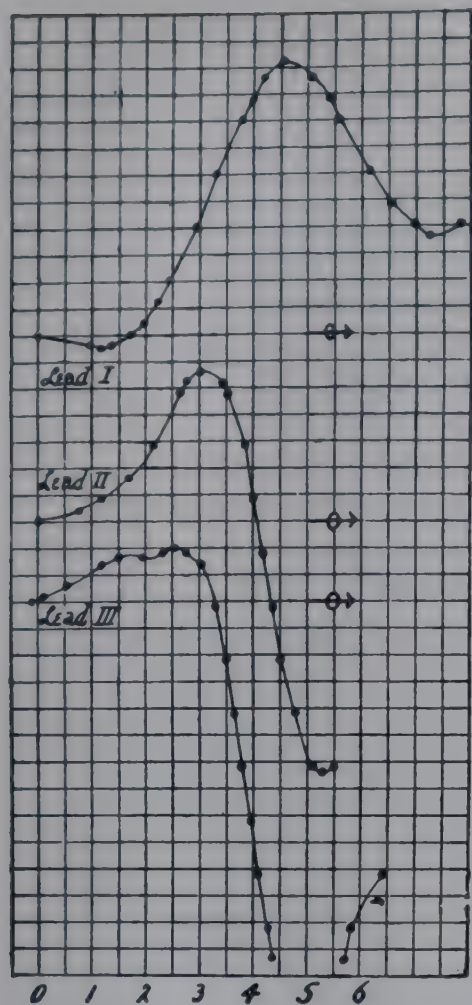


FIG. 76. (Slightly modified from Lewis.) Levocardiogram obtained from a dog after division of the right branch of the auriculo-ventricular bundle. Lower figure shows the directions of the electrical axis in the left ventricle during the initial phases (QRS) of the electrocardiogram, calculated at intervals of 0.005 second. The triangle represents the three leads. The axis rotates in a regular anti-clockwise direction. In the chart above, the potential values recorded in the three leads are plotted at corresponding time intervals. It will be noted that the angle which the electrical axis makes at any instant with a given lead determines the sign and magnitude of the potential difference in that lead. (Ordinates, 1 cm. = 1 millivolt; abscissae, 1 cm. = 0.02 second.)

R wave and increase the S wave in lead III. The more transverse position of the heart tends also to reduce the P and T waves in lead III or to cause inversion of the T wave. Movement of the heart into a more vertical position produces the opposite effects (*right axis deviation*) upon the QRS complex—reduction in the height of the R wave in lead I with an increased depth of the S wave, a small P and an upright T. In lead III the amplitude of R is increased. Thus, in left axis deviation, the electrocardiogram has the characteristics of the so-called levocardiogram, described on page 185, and right axis deviation the characteristics of the dextrocardiogram. Rotation of

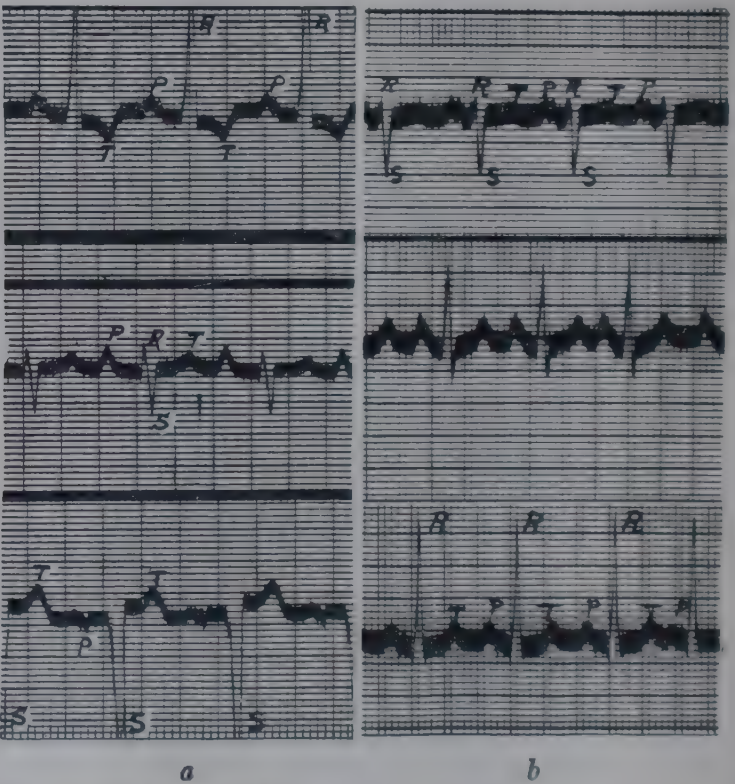


FIG. 77. Abnormal axis deviation. *a*, left ventricular hypertrophy; *b*, right ventricular hypertrophy; vertical lines mark $\frac{1}{4}$ sec. (kindness of Dr. John Hepburn).

the heart may result from tumors, hypertrophy of the ventricle, etc. In the rare developmental anomaly—complete transposition of the heart (dextrocardia)—reversal of all the deflections of the electrocardiogram is seen. The heart lies with its apex pointing to the right. Displacement of the heart as a whole, as by a pleural effusion or pneumothorax, is less likely to produce changes in the electrocardiogram than when it undergoes rotation.

It has been mentioned above that division of one branch of the bundle disturbs the electrical balance of the heart; an abnormal deviation of the electrical axis to the right or left will be a result; interruption of a branch of the bundle by disease causes a similar distortion of the electrocardiogram

(see p. 192). In cardiac hypertrophy and ventricular extrasystoles abnormal deviation of the axis will also occur. Left bundle branch block, left ventricular hypertrophy and right ventricular extrasystoles (see fig. 77 and 82, p. 192) cause left axis deviation; right bundle branch block, right ventricular hypertrophy and left ventricular extrasystoles (see fig. 78) produce right axis deviation.

There has been a considerable amount of discussion concerning the mode of production of the electrocardiographic features of ventricular hypertrophy. The following explanations have been advanced.

(1) That it is due to the *greater mass of muscle*, the electrical changes occurring in the hypertrophied chamber overbalancing those of the normal

of these two factors is the most probable explanation of the characters of the electrocardiogram in ventricular hypertrophy.

THE T WAVE OR END DEFLECTION

There is not unanimity concerning the manner in which the T wave is produced. It is generally accepted, however, that while the QRS complex represents the invasion of the ventricle by the excitatory process, the T wave is produced by the latter's retreat, i.e., during the return of the muscle to the inactive state. Like the QRS complex the T wave is probably a composite effect of the two ventricles, but it is not due to the *arrival* of the excitation wave at the base (p. 183). It is to be remembered that when a muscle is either fully

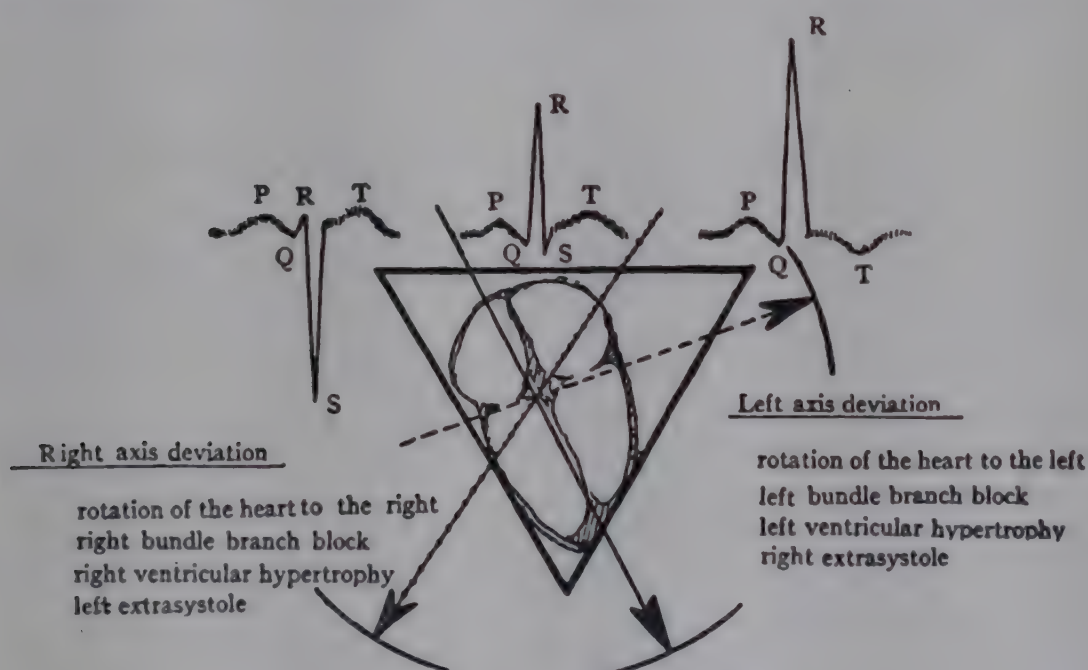


FIG. 78. Diagram to illustrate right (beaded arrow) and left (interrupted arrow) axis deviation. Normal electrical axis shown by arrow with solid shaft. Electrocardiograms are for lead I.

side. This theory has been disproved by the discovery that the electrocardiographic features which were thought to be produced by one ventricle are actually produced by the other (p. 192). In other words, the electrical changes in the *sound* ventricle overbalance those of the hypertrophied side.

(2) *Altered position of the heart.* The greater mass of the hypertrophied ventricle causing rotation of the heart around its longitudinal axis; this probably plays only a minor rôle.

(3) *Slowed conduction over the bundle branch* supplying the hypertrophied ventricle as a result simply of the lengthening of the conduction pathway incident to the enlargement of the ventricular cavity, or to actual injury of the conducting tissue associated in some way with the cardiac disease. According to Barker and associates, one or other

active or completely at rest no potential difference exists between any of its parts and no current flows. The isoelectric interval from S to T represents the period during which the entire ventricular musculature is involved in the excitatory process and is spoken of by Lewis as the *stage of possession*, the Q, R, S and T complexes being referred to as the *stages of invasion* and *retreat* respectively. During the isoelectric period following the T wave (i.e., from T to P) the cardiac muscle is relaxed.

If the order of the retreat of the excitatory process were the same as the order of invasion, i.e., if those regions which were first excited were the first to recover and vice versa, one should expect that the deflection of the retreat, instead of being a single broad wave (T) would be simply a repetition of the QRS complex, but with the several waves reversed. An attempt to explain why the end effect is a single broad deflection is

based upon the belief that the period during which the heart returns to the completely inactive state is slower than the period of invasion of the muscle by the excitation wave. It is believed, moreover, that the excitation wave does not retreat from different parts of the musculature in the same order as it advanced. It does not necessarily disappear first from the region at which it first arrived. It is supposed, on the other hand, that the excitation wave recedes more rapidly from some regions than from others and, as a consequence, relatively large masses of the heart muscle become oppositely charged. It is this state of unbalanced electrical forces which is believed to be responsible for the T wave. In other words, the T wave is explained upon the basis of the theory of distributed potential differences which, as we have seen, is not acceptable as an explanation of the QRS deflections (p. 181). It has been suggested that the active state (negativity) lingers longer in the region of the base than at the apex. In support of the conception of a delay at the base the following observations may be cited.

In the frog, the end deflection is frequently inverted. If the process at the apex is hastened by the application of heat, or that at the base is slowed by cooling, an upright T wave is induced. Heat applied to the base or cold to the apex brings about the reverse effect—inversion of an upright wave. Wilson and Finch showed that the normal human subject gives an inverted T wave after swallowing iced water. The passage of the water along the esophagus cools the apex and delays the disappearance of the excitatory process. The possibility has been suggested that the upright T in the normal electrocardiogram is due to a difference in temperature of the basal and apical regions (the former being in closer proximity to pulmonary tissue, the latter to the liver). It is not known, however, whether or not such a temperature difference actually exists.

A different explanation of the origin of the T wave has been advanced by Hoff and Nahun. They discard the "base-apex" theory, believing that the T wave is caused by interference between the terminal deflections of the dextrocardiogram and the levocardiogram. Normally the terminal deflections of the dextrocardiogram predominate and the T wave is upward in direction, but any condition which tends to prolong the electrical changes of the left ventricle or shorten those of the right was found to cause inversion of the T wave. Thus heating the right ventricle of the dog's heart or cooling the left was found to convert an upright T wave to an inverted one.

Conditions associated with flattening or inversion of the T wave. Vagal and sympathetic stimulation may be followed by inversion of the T wave. Inversion also appears in the early stages of digitalis poisoning; after the administration of adrenaline, quinidine and other drugs; and in acute infections. In these instances there may be little or no alteration in the QRS complex. Inversion of the T wave in leads I and II is taken in general as a very unfavorable sign and frequently accompanies grave cardiac disease. But though it is true that in a series of cases showing persistently an inverted T the duration of life is shorter than in those in which it is upright, the direction of the wave nevertheless cannot be relied upon alone in arriving at the prognosis of an individual case. The deflection may be inverted in temporary and comparatively unimportant conditions, or it may be upright though a fatal termination from cardiac failure is imminent. Flattening or slight inversion of T in lead III is of no significance; it may occur in perfectly normal persons.

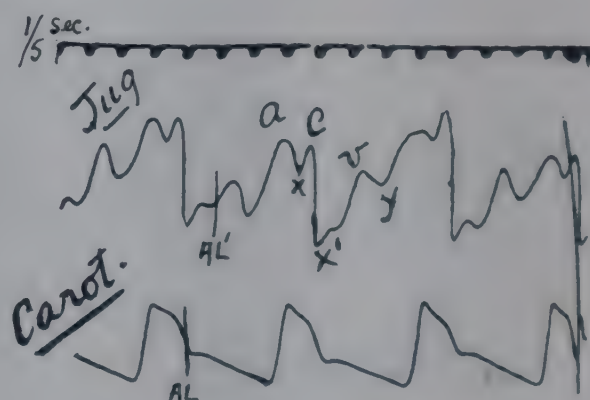


FIG. 79. Upper tracing from jugular vein, lower from carotid artery. AL, alignment marks (after Price).

THE VENOUS PULSE

Pulsation in the large veins at the root of the neck is a normal phenomenon which can be demonstrated by means of special apparatus. It is only under abnormal conditions, however, and then only occasionally that the pulsations are visible to the eye. Valuable information concerning the events of the cardiac cycle from an experimental as well as from a clinical point of view can be gained by a study of jugular pulse records.

The pulsations occurring in the jugular bulb are the result of pressure changes occurring within the right auricle. Since the vein is in direct communication with the interior of the auricle, changes in volume and pressure, which correspond closely to the pressure fluctuations of the intra-auricular pressure curve, are transmitted to the column of venous blood. The intra-auricular pressure is influenced by events occurring not only in the auricle itself but by pressure changes transmitted from the ventricle. For this reason a study of the

waves of a jugular tracing enables the true relations of the different events of the cardiac cycle (auricular and ventricular) to be determined. The jugular tracing though the counterpart in a qualitative sense of the intra-auricular pressure curve, gives no quantitative information, being a record of volume and relative pressure changes only, and no criterion of the absolute pressure values developed in the auricle. The waves *c* and *v* represent ventricular events and are in consequence spoken of as the ventricular complex. The interval between the commencements of the *a* and *c* waves (*a-c* interval) indicates the time elapsing between auricular and ventricular systoles and its duration is an index of the conduction rate between the two chambers.

The waves of the venous pulse are given the same lettering as those of the auricular pressure curve (p. 170). Their main features are

Positive wave *a* due to auricular systole.

Negative wave *x* due to commencement of auricular relaxation.

Positive wave *c* due to ventricular contraction and bulging of A-V valves into the auricle.

Negative wave *x*¹ due to drawing down of A-V septum and the discharge of blood from the thoracic cavity.

Positive wave *v* due to filling of auricle which is closed below by A-V valves.

Negative wave *y* due to opening of A-V valves and emptying of auricle into the ventricle.

In figure 79 is shown a typical venous pulse. The waves show their distinctive characters which may be recognized almost at a glance. Venous tracings from a clinical case, however, are frequently atypical and present a confused series of irregular waves which are impossible to identify by mere inspection. Sometimes successive waves, for instance, *a* and *c*, or *v* and *a*, are merged together. At other times certain waves are absent. We must then have recourse to some method

of distinguishing the various fluctuations in order to interpret the tracing. An arterial tracing serves as a key. In figure 64 (p. 171) the intracardiac, venous, and arterial curves are accurately superimposed; that is, they all commence at the same instant. Consequently synchronous events lie along vertical lines intersecting the several tracings. In the case of the jugular tracing the commencement of the upstroke of the carotid is synchronous with the commencement of the *c* wave. The upstroke of the carotid or of the radial artery is practically always a landmark which is clearly discernible. Therefore, if one could take a venous tracing accurately superimposed with a carotid tracing, a vertical line drawn through the commencement of the upstroke of the latter would when extended through the venous curve indicate the commencement of the *c* wave. It is not feasible, however, to do this, but the time relations of the two writing levers can be correlated by means of what are known as *alignment marks*. That is, while the writing surface is at rest the two levers are given a light tap so that each makes an upright mark. The marks are used as points from which measurements may be made and the two tracings synchronized in an indirect way. Thus (cf. fig. 79) the distance from the alignment mark AL to the carotid upstroke is measured. This distance is then laid off upon the venous tracing commencing from the alignment mark AL. It will indicate a point on the jugular tracing corresponding to the commencement of the *c* wave. When the arterial tracing is taken from the radial, as is most commonly done, the procedure is the same, except that a distance representing $\frac{1}{10}$ second, obtained from the time tracing, must be deducted from the measurement. This is the difference in the times of arrival of the pulse at the carotid and the radial. The instrument employed for the clinical registration of jugular and arterial pulses, and originally devised by Mackenzie, is known as the *polygraph*.

In determining the length of the arterial pulse wave (p. 150) a procedure similar to that just described is followed in timing the successive arrival of the wave at two points in the arterial tree.

CHAPTER XXIV

DISORDERS OF THE HEART BEAT AND THEIR INVESTIGATION BY GRAPHIC METHODS

The following is a convenient classification of cardiac irregularities:

A. Affections of rhythm due to impaired conduction through the A-V bundle and its ramifications

I. Stem of bundle

- (1) Delayed conduction
- (2) Missed beats, partial heart block
- (3) Complete heart block

II. Bundle branch defects

B. Affections due to abnormal impulse formation

I. Extrasystoles

- (1) Ventricular
- (2) Nodal
- (3) Auricular

II. Paroxysmal tachycardia

Auricular, nodal and ventricular

III. Auricular flutter

IV. Auricular fibrillation

V. Ventricular fibrillation

C. Alternation of the heart

D. Affections due to vagal influences

- I. Sinus arrhythmia
- II. Phasic irregularity
- III. Sinus bradycardia
- IV. Sino-auricular block

A. AFFECTIONS OF RHYTHM RESULTING FROM IMPAIRED CONDUCTION

I. IN THE A-V NODE OR STEM OF THE BUNDLE—AURICULO-VENTRICULAR BLOCK

In animals, conduction from auricle to ventricle can be depressed or blocked by crushing, cutting, or the application of cold to the A-V bundle. This strategic point in the pathway of the excitation wave is also attacked by disease, and conduction through it may be depressed or completely abolished. Depression of conduction through the node or bundle varies in degree. Three stages are recognized.

(1) Delayed conduction

In this stage conduction is merely slowed; every impulse reaches the ventricle. The intervals between the auricular and ventricular systoles (A-V_s intervals) are lengthened and may have a

duration of 0.5 second, though, as a rule, they are considerably shorter than this. The condition can be recognized only by means of the electrocardiograph or a venous pulse tracing. Lengthening of the P-R interval in the former tracing, or of the *a-c* interval in the latter, beyond the normal maximum of 0.2 second is taken to indicate delayed conduction (fig. 80).

(2) Missed beats—partial heart block

When impaired conduction reaches a certain degree, impulses from time to time fail to reach the ventricle, and a beat is missed. The auricular beats are perfectly regular, and in this way the condition differs from sino-auricular block (p. 204). A ventricular beat may be missed only occasionally and at irregular intervals. The P-R or the *a-c* intervals may generally, though not invariably, be seen to lengthen progressively for several heart cycles preceding the dropped beat. The interval of the cycle succeeding the missed beat is shortened again to near the normal length. In a further stage of the condition the beats are dropped more frequently and may be spaced either at regular or irregular intervals in the tracing. When the grade of block is still more advanced, impulses fail to penetrate the bundle after every second auricular beat; or three, or even four auricular contractions may occur before an impulse reaches the ventricle, i.e., the ventricle responds only to every third or fourth auricular beat. So, an auriculo-ventricular rhythm becomes established in which the two chambers beat in the ratio of 2:1, 3:1, or 4:1. The first of these is seen most frequently, the second is the least common (fig. 80).

(3) Complete heart block

When the A-V node or bundle offers an absolute barrier to the passage of the impulse, the dissociation of the rhythms of the two ventricles is complete (fig. 81). The auricle beats at its own rate of about 70 per minute and the ventricle at its inherent rate of about 35. The latter is then spoken of as the idio-ventricular rhythm. Both ventricles beat simultaneously. This fact suggests that when the ventricle assumes this rate it is

under the control of some single region possessing the power of rhythmical activity. From experimental investigation it appears that the controlling center is the A-V bundle below the site of the lesion. The speed with which a particular region of the heart can develop and discharge impulses apparently determines its ability to dominate

Partial and complete heart block are accompanied by changes in the rhythm of the arterial pulse. When beats are missed occasionally the pulse intermits either at regular or irregular intervals. In the more fully developed conditions marked slowing (bradycardia) of the pulse occurs. Visible pulsations in the veins at the root of the neck may occur, for the auricle, in con-

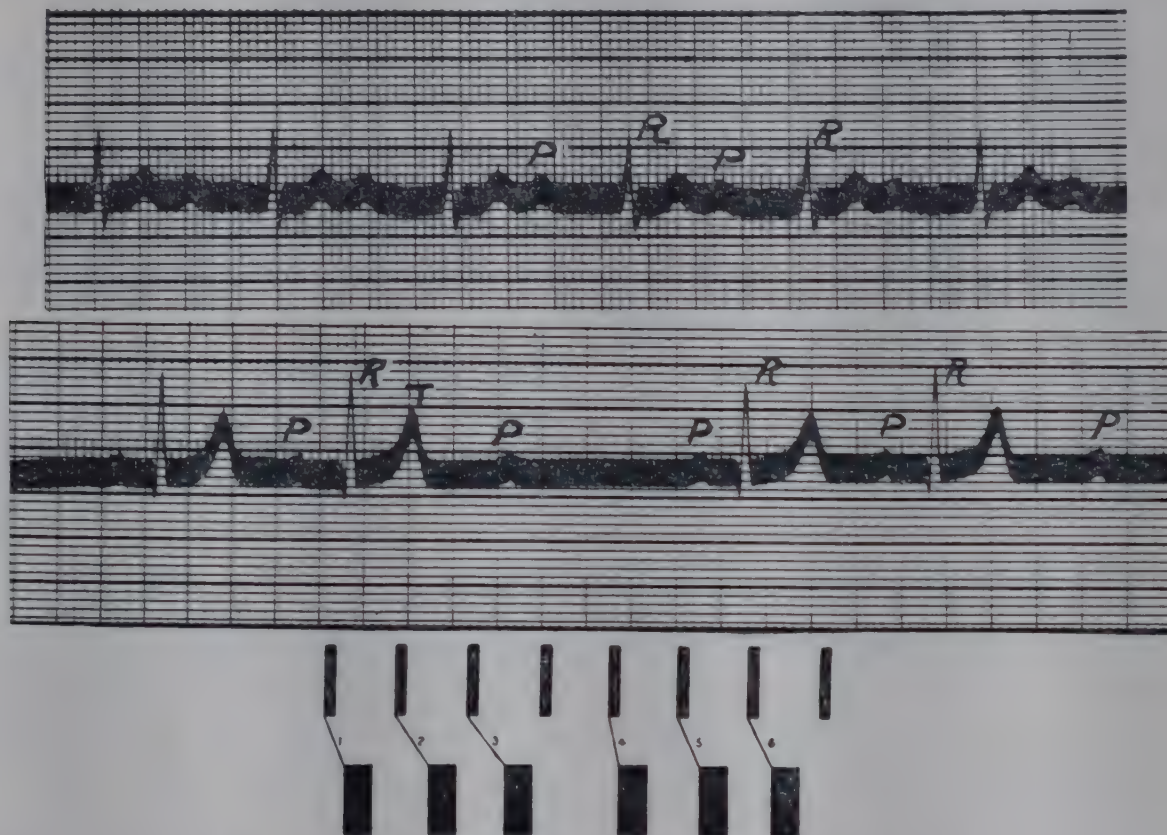


FIG. 80. Upper tracing, delayed conduction, lead I. Lower tracing, incomplete heart block, lead I (missed beats). (Kindness of Dr. John Hepburn.) The diagram below (after Lewis) represents incomplete heartblock. The thin rectangles, A, represent contractions of the auricle, the thicker ones, V, contractions of the ventricle. The obliquely directed lines represent conduction over the A.V. bundle; the slower the conduction rate the more oblique the line. The gaps in the lower rectangles indicates missed beats of the ventricle. It will be noted that delay in conduction increases progressively in successive cycles until a beat is missed. Heavy vertical lines = $\frac{1}{2}$ sec.

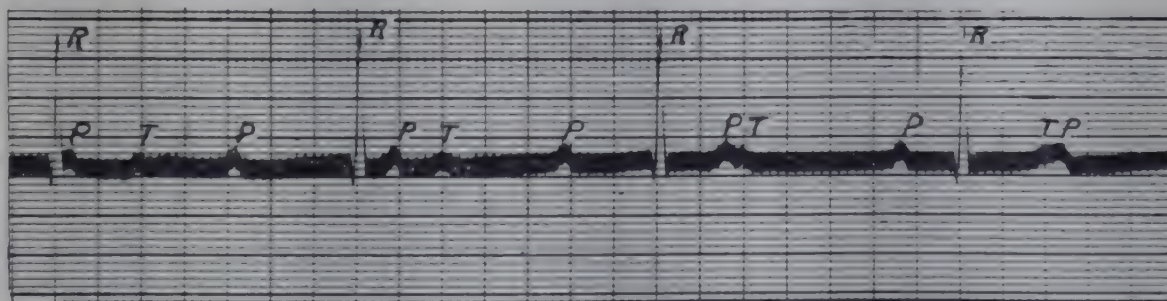


FIG. 81. Complete heart block, lead I (kindness of Dr. John Hepburn).

other regions. It has been mentioned that when a region of higher rhythmicity is destroyed or isolated the region next in order of rhythmical power assumes the rôle of pacemaker (p. 163, 206). When, for instance, the S-A node is destroyed or isolated the A-V node assumes control, and when this or the upper part of the bundle is separated from the tract of tissue below, the lower lying portion takes over the government of the ventricular rate.

tracting upon a larger volume of blood accumulated as a result of the infrequency of the ventricular contractions, causes a pronounced wave to be transmitted along the jugular. A certain proportion of the venous pulsations may be seen to be unassociated with an arterial pulse. Sometimes a sound may be heard over the heart at the time of the isolated venous pulsation since the auricular contraction is unusually forceful and the sound vibrations thus set up are not smothered by the first heart sound which, in the normally beating heart, follows so closely upon auricular systole.

The venous pulse tracing and electrocardiogram show characteristic features. The *a* and P waves of the respective records occur at the usual times, but the ventricular complex (*c* and *v* in the venous curve and QRS and T in the electrocardiogram) is absent, a gap appearing in the tracing each time a beat of the ventricle is missed. In incomplete heart block, as one would expect, a relationship between a ventricular complex and a preceding auricular wave can always be made out, whereas in complete block there is no relationship. In the venous pulse, for example, the *a* and *c* waves may occur simultaneously, and produce a large *a + c* wave. Or the *a* and *v* waves may coincide. Corresponding effects are produced upon the electrocardiogram.

Temporary heart block may result from various toxic agents, e.g., digitalis, strophanthus, quinidine, etc., which exert a specific effect in depressing auriculo-ventricular conduction. Heart block may be a sequel or an accompaniment of several acute infectious maladies, e.g., diphtheria, rheumatic fever, etc. It is produced in animals by asphyxia (p. 214). Increased vagal tone is sometimes responsible for delayed conduction over the A-V bundle. Partial heart block is not uncommonly seen in the course of rheumatic fever and is then, in many instances, of vagal origin, being temporarily abolished by atropine.

Stokes-Adams syndrome. This condition was first described by Adams (1827) and later by Stokes (1842). Its features are a slow pulse and syncopal attacks or convulsive seizures, usually epileptiform in character. The term includes any condition of vascular origin in which these features are associated, and it is probable that the underlying morbid state upon which the syndrome depends is not identical in all instances (see also carotic sinus, p. 241). In the majority, however, the slowed cardiac action is the result of heart block, and the cerebral symptoms are the direct result of the bradycardia. The prolonged pause between beats permits the diastolic pressure to fall to a low level; the blood supply to the cerebral centers suffers in consequence. Hardening of the larger arteries or aortic regurgitation, etc. when present in association with heart block, must enhance the effect of the bradycardia upon the diastolic pressure. That heart block alone is capable, however, of causing the syndrome was shown by Erlanger and Blackman (p. 166) who reported similar syncopal and convulsive seizures in dogs after division of the bundle. Adrenaline or ephedrin has been employed with some success.

II. BUNDLE BRANCH DEFECTS—INTRA-VENTRICULAR BLOCK

When one or other of the primary divisions of the bundle is blocked by disease the impulses reach the muscle of the two ventricles asynchronously. The ventricle of the sound side is activated a fraction of a second before the other. The affected

ventricle is excited later by the escape of the impulse from the healthy side through the septum (p. 185). The imbalance between the electrical effects in the two ventricles produces characteristic electrocardiographic features. Bundle branch block is most commonly associated with coronary disease. The left branch of the bundle is involved five times more frequently than the right (see also p. 186).

From his experiments upon animals (p. 185) Lewis concluded that a clinical record having the characters of a levocardiogram (main deflection of the QRS group *upward* in lead I and *downward* in lead III) or of a dextrocardiogram (main deflection of the QRS group *downward* in lead I and

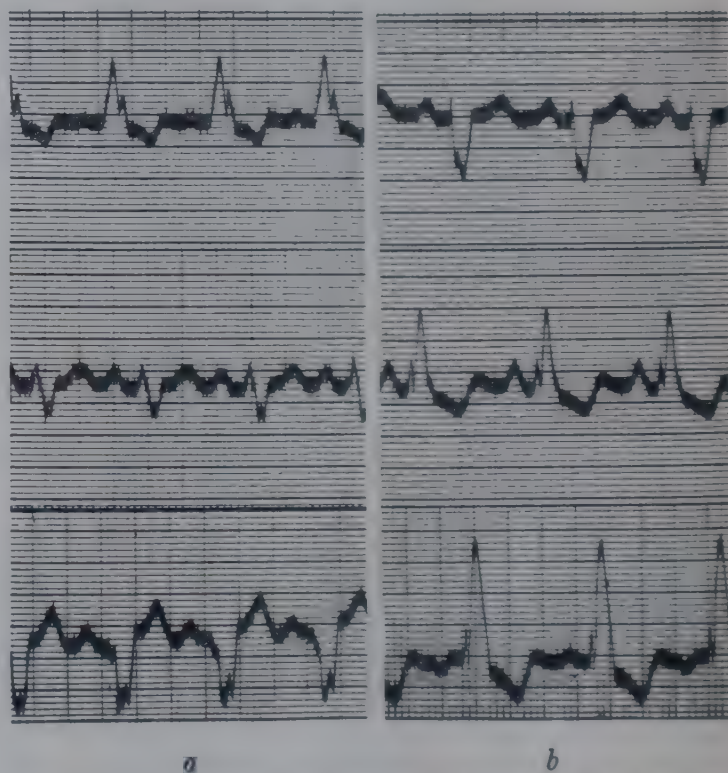


FIG. 82. *a*, left bundle branch block; *b*, right bundle branch block. Note lengthening of QRS. Compare with fig. 79 (kindness of Dr. John Hepburn).

upward in lead III) was due to disease of the *right* or *left* bundle branch respectively. Reports of post-mortem examinations of the conducting system of subjects which had shown the characteristics of a levocardiogram during life also supported this conclusion since the *right* branch was said to be diseased. Barker, MacLeod and Alexander, however, stimulated the surface of the exposed human heart and obtained extrasystoles (p. 193) whose characters indicated that the so-called levocardiogram is produced by the right ventricle and the dextrocardiogram by the left. They conclude therefore that a record in which the main initial deflection is upward in lead I and downward in lead III—the so-called levocardiogram—is due to disease of the *left* bundle branch and that an

electrocardiogram in which the main initial deflection is downward in lead I and upward in lead III—the so-called dextrocardiogram—is due to disease of the *right* branch. In other words, the electrocardiogram which has hitherto been ascribed to a lesion of the right branch is actually due to disease of the left branch and vice versa (see fig. 82). The difference between the results

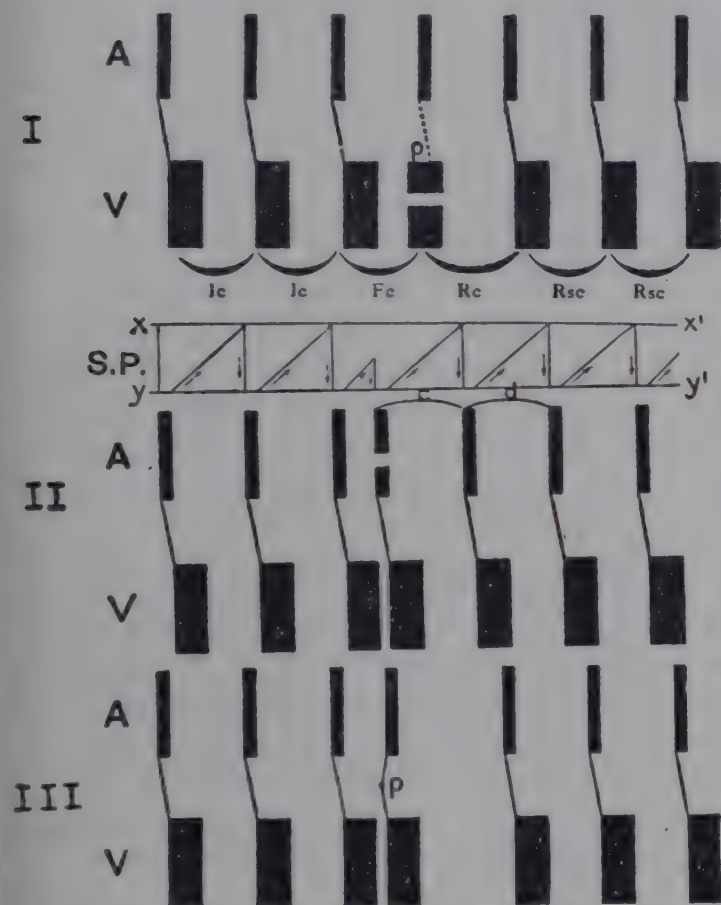


FIG. 83. (After Lewis). I. A diagram illustrating disturbance of the heart's mechanism when a systole is caused by exciting the ventricle during diastole. Ic, initial cycle; Fc, forced or extrasystolic cycle; Rc, returning cycle; and Rsc, restored cycles. p is the premature or forced beat. Note that the auricular rhythm remains undisturbed. The forced and returning cycles are together equal in length to two initial cycles. II. A diagram illustrating the events when a premature contraction is excited from the pacemaker. Stimulus production in the tissue which originates the heart rhythm is indicated by the line S.P.; the impulse is supposed to discharge when it reaches the line xx' and to fall at each contraction of the heart to the level yy' . c and d are equal in length. III. A diagram illustrating a premature beat arising in the A-V node.

of experiments upon the dog and clinical cases is ascribed by Wilson and his associates to the fact that the direction of the anatomical axis of the heart and the inclinations of the intraventricular septum in this animal are not the same as they are in the human subject. Strands of conducting tissue also cross the right cavity of the canine heart which are absent in the human heart. Roberts and associates in experiments upon the cat and the monkey, also found that division of the right branch produced a record in which the main

initial deflection was downward in lead I and upward in lead III. Opposite effects resulted from division of the left branch.

The direction of the T wave (upward or downward) is usually opposite to that of the main deflection of the QRS group. Thus in disease of the right branch the T wave has the normal direction in lead I but is inverted in lead III. Bundle branch disease is of the gravest significance, the subject rarely surviving many months after it has been discovered. The electrocardiograph is the only means by which it can be recognized. Distortion of the electrocardiogram similar in type to that seen in bundle branch block occurs in other conditions (p. 185) but a distinguishing feature of the former is lengthening of the QRS complex beyond the normal maximum of $\frac{1}{10}$ second. In disease of the left branch of the bundle the Q-E interval is prolonged owing to the lag in ventricular ejection.

B. DISTURBANCES OF RHYTHM DUE TO ABNORMAL IMPULSE FORMATION

I. EXTRASYSTOLES OR PREMATURE CONTRACTIONS

An extrasystole can be induced experimentally by stimulating the cardiac muscle at any time except during its phase of absolute refractoriness (p. 155). Extrasystoles occur in the human heart as a result of some abnormal process of impulse formation. Though extrasystoles may be associated with organic heart disease they more frequently occur in its absence; they may then be of reflex origin initiated from the abdominal viscera or be due to some form of intoxication, e.g., digitalis, chloroform anesthesia, hyperthyroidism, excessive smoking, etc. Beattie, Brow and Long produced extrasystoles in cats by stimulation of the hypothalamus (p. 883), and their occurrence in man following brain lesions has been reported by Lucke and by Korth, which indicates that in some instances they are of central origin. The auricle or the ventricle may be the site of origin of the premature contraction, or the extra impulse may arise in the A-V node (see diagrams, fig. 83).

(1) Ventricular extrasystoles

The premature contraction occurs after the normal ventricular beat has ceased and the muscle has recovered from its absolute refractory state. It is not preceded by an auricular contraction, and is not dependent upon an impulse received from the upper chamber (fig. 84). The premature contraction is followed by a long pause. This is

usually of just sufficient duration to cause the succeeding normal ventricular beat to occur at the instant that it would have occurred had there been no premature contraction. The cause of this *compensatory pause* has been explained elsewhere (p. 155). Briefly, it is due to the normal impulse reaching the ventricle when the muscle is still refractory as a result of the premature beat. The interval between the normal beat and the one following the premature contraction is therefore equal in length to two normal cardiac cycles (fig. 83, I). Sometimes, however, when the extrasystole occurs early in diastole and the heart rate is slow there may be no compensatory pause. The auricular impulse then reaches the ventricular muscle after it has recovered from the refractory state resulting from the premature beat; the auricular impulse therefore brings about a response at, or (as a result of some lengthening of the A-V₁ interval following the premature beat) slightly

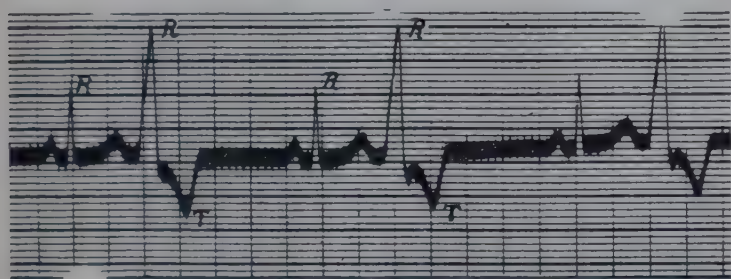


FIG. 84. Ventricular extrasystoles (bigeminal pulse, p. 196) arising in right ventricle—left axis deviation (p. 186). (Kindness of Dr. John Hepburn.)

after the usual time. The normal ventricular systoles are then all equally or nearly equally spaced and the extra contractions are interposed here and there between them. That is, the time interval from the normal beat preceding the extra contraction to that following it is of normal length or but slightly lengthened. Premature beats of this nature are called *interpolated extrasystoles*.¹

(2) Auricular extrasystoles

The premature contraction arises in the auricle at some point outside the S-A node. The abnormal impulse reaches the ventricle along the usual paths and evokes a ventricular contraction, unless the auricular beat is so premature that sufficient time has not elapsed to permit the recovery of the ventricular muscle from its refractory state. The latter, except for its time relations, is approxi-

¹It should be noted that except in the case of interpolated beats there is not an extra or additional beat, as the term extrasystole seems to imply. The premature beat, in effect, displaces the normal beat.

mately normal. An auricular extrasystole, therefore, causes a premature contraction of the whole heart. The premature auricular beat prevents the occurrence of the next normal auricular impulse and the pause of the auricle which follows the abnormal auricular contraction is usually precisely equal to a normal interval. This fact has been explained upon the assumption that, normally, impulse formation in the S-A node is the result of the liberation of energy which has been built up during the previous quiescent period. Upon the occurrence of the abnormal impulse this store of energy, accumulated for the normal impulse, is discharged and a definite time interval must elapse before it is again built up to the required level. (See fig. 83, II.) Sometimes, however, the interval following the premature contraction is slightly lengthened, suggesting that the rate at which the S-A node builds up its store of energy is lowered. In any event, there is rarely a long (compensatory) pause following the beat of the *ventricle*, the interval between the two normal beats, i.e., from the beat preceding to the one succeeding the premature contraction, being nearly always shorter than two normal cycles. In other words, the normal auricular impulse following the premature auricular contraction upon reaching the ventricle does not "miss-fire," as in the case of ventricular extrasystole, but calls forth a response from the ventricle.

(3) Nodal extrasystoles

Extrasystoles occur sometimes as a result of impulse formation in the A-V node or supraventricular part (stem) of the bundle. On account of its central position between the two chambers, impulses arising in the A-V node pass upward and downward to cause simultaneous or nearly simultaneous responses from auricle and ventricle. Sometimes the ventricular contraction may actually occur first, in which case it is suggested that the impulse has arisen in the stem of the bundle and so has its course to the ventricular muscle considerably shortened. The extra cycle is usually, though not invariably, followed by a compensatory pause (fig. 83, III).

In rare instances extrasystoles arise as a result of abnormal impulses initiated in the sino-auricular node—*sinus extrasystoles*. Except for the interposition of the extra beat the rhythm of auricles and ventricles is but little disturbed. The interval following the extra beat is normal in length or slightly shortened.

The effects of extrasystoles upon the characters of the electrocardiogram and of the arterial pulse

THE ELECTROCARDIOGRAM. In *ventricular extrasystoles* the electrocardiogram shows irregularity in the spacing of the ventricular complexes. The following characteristics are found:

(1) The intervals between the R wave caused by the premature beat and the corresponding waves of the normal beats preceding and following it, respectively, are altered in length. The interval between the last normal R wave and the premature R wave is short, while the interval following this to the next normal R wave is prolonged—compensatory pause. The time elapsing between the two normal R waves is usually equal to the length of two normal cycles.

(2) The premature R wave is not preceded by a P wave. Since the premature ventricular contraction occurs unrelated to auricular systole it frequently happens that a normal contraction of the auricle occurs about the same time as the ventricular extrasystole. P and R waves then become fused. At other times the P wave follows closely upon the premature R wave.

(3) The P waves are equally spaced and some appear which are not succeeded by a ventricular complex (refractory period of the ventricular muscle). In the case of the *interpolated* type of extrasystole, however, each P wave is followed by an R wave, and no long pause is seen.

(4) Ventricular extrasystoles also show abnormalities of the QRS complex which distinguish them from premature contractions of auricular or nodal origin. An impulse arising in the heart below the point where the bundle forks will activate one ventricle slightly in advance of the other. It is to be expected then that the QRS deflections of the electrocardiogram will be a record of unbalanced electrical effects. This is actually the case (fig. 84). In other words, if the extrasystole arises in the left ventricle its record will be deformed much in the same manner as that already described (p. 192) for right bundle branch block (right axis deviation—main initial deflection downward in lead I and upward in lead III). If the premature beat arises in the right ventricle the electrocardiogram will show the features of a left branch defect (left axis deviation—main initial deflection upward in lead I and downward lead III).

In *auricular extrasystoles* the electrocardiogram shows disturbances in the timing of both the auricular and the ventricular complexes, but, as

already mentioned (p. 194), a normal or only a slightly lengthened pause follows the extra beat. The P waves are unequally spaced but each is followed by a ventricular complex. The abnormal auricular wave may coincide with and be buried in the QRS complex of the preceding normal cycle.

The records of *extrasystoles arising in the A-V node* or supraventricular part of the bundle are variable according to the timing of the auricular and ventricular contractions. When the auricles and ventricles are excited simultaneously the P and R waves become fused. When the two chambers are not activated simultaneously, the P precedes the R wave by a short interval, or the order of the waves may be reversed (R-P interval).

THE ARTERIAL PULSE. It has been demonstrated that several long-recognized irregularities of the pulse are the result of extrasystoles. For example, in the irregularity known as *intermittent*

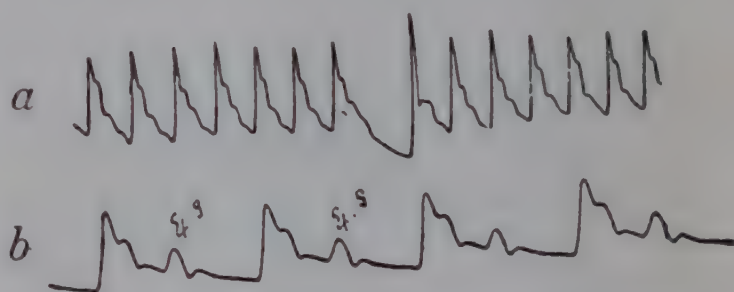


FIG. 85. (After Price.) a, intermission of the pulse; b, pulsus bigeminus, due to a single extrasystole with its succeeding compensatory pause occurring regularly after each normal beat. *Ex.S.*, extrasystole.

pulse there appear from time to time relatively long intervals during which no beat is felt in the radial (fig. 85, a). The intervals are most pronounced when a premature contraction of the ventricle which is too weak to open the semilunar valves occurs. This most commonly happens when the heart muscle receives the abnormal impulse during the earlier part of its relative refractory phase. The premature beat may be detected by hearing a faint first heart sound which is not succeeded by a second sound (p. 175). No pulse is produced in the radial at the time, nevertheless the extrasystole may be followed by a compensatory pause, and graphic records show as a rule that the gap in the radial tracing is just equal to two normal cycles. That is, a beat is dropped completely from the arterial record. The detection of an extra contraction of the ventricle, however, enables the irregularity to be distinguished from the missed beats of partial heart block (p. 190) which may give an arterial tracing with similar characters.

If ventricular extrasystoles which fail to open the semilunar valves are repeated after each normal beat, the long intervals separating the latter will cause pronounced slowing of the pulse rate. The pauses between the arterial pulses are doubled in length and the pulse frequency as a consequence is reduced to half the normal. Bradycardia produced in this way and sometimes termed *false heart block* is distinguished from true heart block by a study of the venous pulse or the electrocardiogram which reveals the extra ventricular complexes; or the faint sounds of the extra contractions may be heard upon auscultation.

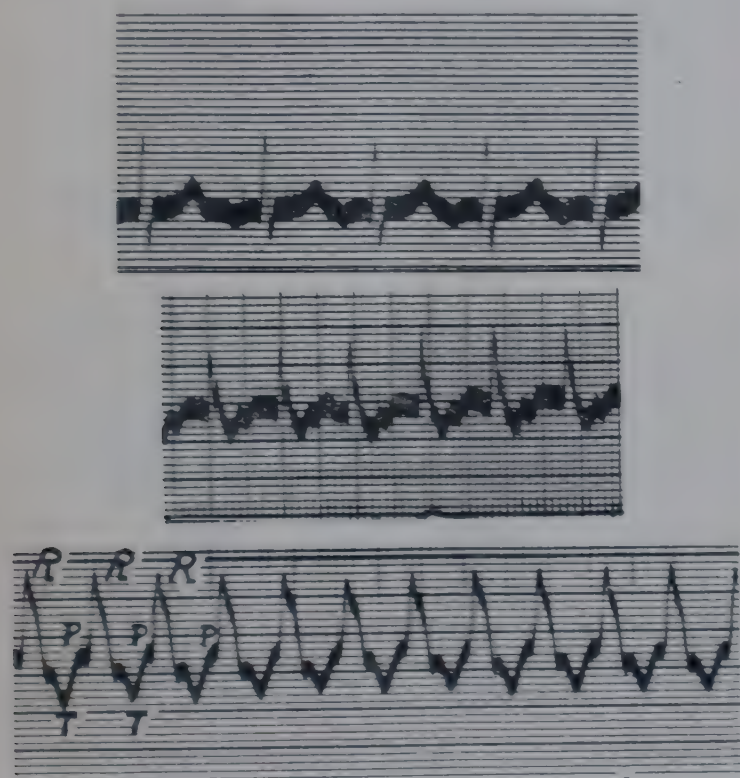


FIG. 86. Top tracing, auricular tachycardia; middle tracing, nodal tachycardia; bottom tracing, ventricular tachycardia. (Kindness of Dr. John Hepburn.)

When the extrasystoles are forceful enough to open the semilunar valves, and occur regularly one after each normal systole, paired pulse beats, each couple being followed by a long pause, are felt in the radial (fig. 85, b). This type of pulse irregularity, which is sometimes seen following overdosage with digitalis, is called the *bigeminal pulse* (*pulsus bigeminus*).

II. PAROXYSMAL TACHYCARDIA

This may be defined as a condition in which the rate of the heart is greatly accelerated for a longer or shorter period without obvious cause. The rate varies in different cases from 120 to 250 per minute. The onset of the paroxysm is sudden and the increased rate is maintained for a variable length of time with perfect regularity, successive

cycles usually not varying in length by more than a hundredth of a second. The paroxysm lasts for only a few beats in some instances, in others it persists for a few minutes, hours or even days, though attacks of more than ten days duration are very rare (Lewis). The attack ceases as abruptly as it commenced, the heart resuming its normal rate almost instantly.

The paroxysm, it is believed, consists of a series of rapidly recurring extrasystoles which completely submerge the physiological rhythm. The site of origin of the extrasystoles, as in the case of single premature beats, may be in the *auricle*, the *A-V node or stem of the bundle*, or in the *ventricle* (fig. 86). The auricular type is the most common; each auricular impulse spreads to the ventricle and causes a contraction whose features as indicated by the electrocardiogram are normal. The P wave is frequently inverted.

When the impulses arise in the A-V node or supra-ventricular part of the bundle, the P-R intervals of the electrocardiogram are shortened. Inversion of the P waves is common. Or, the contractions of the two chambers may be simultaneous, the P waves being then buried in the ventricular (QRS) complexes. Again, the contraction of the ventricle may occur before that of the auricle; it then sometimes happens that a progressive lengthening of the intervals between the R and P waves (R-P interval) of the electrocardiogram is seen; ultimately an auricular beat is missed. This is termed *reversed heart block*. In other instances, as the R-P intervals reach a certain length, a contraction of the ventricle occurs prematurely, and is not followed by a contraction of the auricle. It is thought that the ventricular contraction is caused by the same impulse that caused the preceding auricular beat. That is, the impulse arising in the node first excites the auricle, then re-enters the junctional tissue, which has now recovered from its refractory phase, and passes downwards to the ventricle. This is spoken of as *reciprocal rhythm*.

When the impulses arise in the ventricle the QRS complexes have the characteristics of those caused by ventricular extrasystoles (p. 193). The auricular rhythm is usually undisturbed but occasionally it is abnormal, for, when a series of rapidly recurring contractions arises in the ventricle the impulses may pass along the bundle in a retrograde fashion and activate the auricle to the exclusion of the normal impulse. In other words, the ventricle then sets the pace and the auricle follows. In such instances the P waves are inverted and succeed the QRS deflections, or are buried in the ventricular complexes as in the nodal type mentioned above.

III. AURICULAR FLUTTER

There are two forms of this disorder, *pure* and *impure flutter*. In both types the auricle beats

at the phenomenally rapid rate of from 200 to 400 beats per minute, but in pure flutter the rhythm is regular, in impure flutter it is irregular. Flutter differs from paroxysmal tachycardia in the following particulars.

(a) The auricular rate of beating is usually much greater than that seen in paroxysmal tachycardia.

(b) The disorder is of much longer duration, persisting unchanged for months or years, though it is sometimes transient.

(c) The ventricle fails as a rule to follow the rate of the auricle; a state of relative heart block becomes established as a result of the comparatively long refractory phase of the junctional tissue.

(d) It is produced (p. 199) by the passage of the impulse over one or more circular pathways—*circus movement*.

Auricular flutter may become converted to paroxysmal tachycardia.

In pure flutter the rhythm is remarkably regular (fig. 87). The lengths of the auricular cycles vary

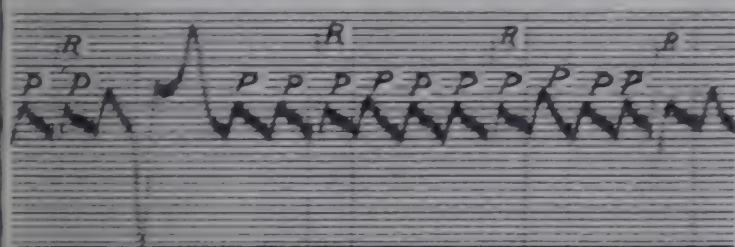


FIG. 87. Pure flutter with a ventricular extrasystole (kindness of Dr. John Hepburn).

no more than a few thousandths of a second over comparatively long periods. In impure flutter this constancy of cycle length is not seen and varying degrees of irregularity occur. In flutter the auricular walls do not completely relax. That is, though the proportion of active to inactive fibers varies during the rapid beating, at no one time are all the fibers in the relaxed state (p. 170). In the electrocardiogram, therefore, the level of the tracing between the P waves lies for the most part above the isopotential line, only touching the latter for an instant. The level of the tracing is continually changing and the electrical changes of the auricle are carried over to alter the form of the ventricular complex. On the other hand, the fibers are never all contracted at the same time, so that auricular systole as well as diastole is incomplete.

The ventricle rarely keeps pace with the racing auricle, the refractory phase of the conducting tissue being longer as compared with that of the auricular muscle. As a consequence, a state of

relative heart blocks develops and an auriculo-ventricular rhythm of 2 to 1, or less frequently, of 3 to 1 or 4 to 1, becomes established. Should the ventricle respond to each beat of the auricle, as occasionally happens, serious circulatory disturbances follow; ventricular diastole is so shortened that the ventricle receives a greatly reduced load of blood. The output of the heart may be so reduced as a result that loss of consciousness resulting in death may follow.

IV. AURICULAR FIBRILLATION

This condition so far as fundamental causes are concerned may be looked upon as an advanced stage of flutter. The auricular muscle is the seat of incomplete contractions which recur at a frequency of from 400 to 600 per minute. So incomplete are the contractions and so rapidly are they produced that the individual beats are scarcely distinguishable from one another. The auricular cavity is never emptied of blood and its wall is a quivering sheet of muscle. Auricular fibrillation is the most common of all the serious cardiac irregularities, being associated, according to Lewis, in 60 to 70 per cent of all cases of cardiac failure in hospital practice. It is most frequently seen in mitral stenosis and in thyrotoxicosis (p. 675). It rarely occurs in the absence of myocardial disease.

Only a proportion of the auricular impulses pass through the A-V bundle and activate the ventricle. The relatively long refractory period of the conducting tissue shields the ventricle from the high rate of the auricular beating. The arterial pulse, nevertheless, is usually considerably faster than the normal (100 to 150) though it may be normal or even slowed. Those impulses which reach the ventricle do so in a somewhat haphazard manner, and indeed one of the most characteristic features of fibrillation of the auricles is absolute irregularity in the rate and force of the ventricular beats. These features are expressed in the terms "*delirium cordis*," "*complete irregularity of the pulse*" or "*perpetual arrhythmia*," which were applied to the condition before its true nature was recognized. A proportion of the heart beats are frequently so weak that they fail to cause a pulse in the radial. The apex beat is therefore much more rapid than the pulse. The former, for example, may be 150 and the latter only 60 or 70. The difference is called the *pulse deficit*. With treatment and improvement in the condition of the cardiac muscle the pulse rate therefore may increase.

The venous pulse in auricular fibrillation is of the ventricular form, a waves are absent, being represented by a series of rapid vibratory waves (f waves). Similarly in the electrocardiogram, small rapid undulations replace the P waves (fig. 88).

V. VENTRICULAR FIBRILLATION

The ventricular muscle may pass into a state of rapid, tremulous and ineffectual contractions closely similar in nature to the condition just described as occurring in the auricle. In animals, ventricular fibrillation may be initiated by direct electrical stimulation of the ventricular muscle, as was first shown by Ludwig in 1850. Mechanical stimulation of the ventricle, especially by pricking the tissue in the A-V groove, ligation of a coronary artery (Porter) or certain chemicals and drugs in excess, e.g., digitalis or calcium chloride, may induce fibrillation. Levy found that chloroform anesthesia renders the hearts of experimental animals (cats) highly susceptible to fibrillation.

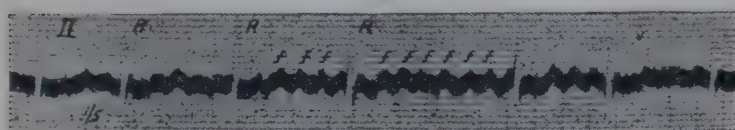


FIG. 88. Auricular fibrillation, lead 2 (after Lewis).

A mere touch of a finger or instrument, the stimulation of a sensory nerve, section of the vagi or their paralysis by atropine, may set the ventricle fibrillating. The heart behaves as though sensitized by the anesthetic and ready at the least provocation to fibrillate. Adrenaline was found to greatly enhance the effect of chloroform—a fact which indicates the danger of adrenaline administration while a subject is under the effect of this anesthetic. Fibrillation may also ensue spontaneously under chloroform and Levy found that the condition is more likely to supervene when the animal is passing from deep to light anesthesia. Cyclopropane, like chloroform, has the effect of sensitizing the heart to the action of adrenaline in inducing ventricular tachycardia and fibrillation, but these cardiac irregularities are rarely seen under ether anesthesia. Quinidine reduces the susceptibility to fibrillation during cyclopropane anesthesia.

The effects of ventricular fibrillation upon the circulation are incomparably more serious than those of the corresponding auricular condition. This is evident when the importance of the two musculatures in the dynamics of the circulation are compared (p. 170). In fibrillation of the

lower chamber the propulsive force of its contraction is practically abolished and the circulation comes to an end; death follows within a few minutes.

From experiments upon animals it is believed that many instances of cardiac failure in patients under chloroform are due to fibrillation of the ventricles. This is generally considered to be of sudden onset, but it has been shown that when the condition is induced in animals by chloroform it is frequently ushered in gradually. A solitary extrasystole first occurs, which is followed after a time by coupling, tripling, and later by short runs of extrasystoles. Longer paroxysms of rapid beating follow. Finally as the tachycardia becomes more rapid it merges into fibrillation.

When fibrillation is induced suddenly as by electric shock its development may be somewhat different. According to Wiggers and his associates, only the first contraction is a true premature beat; those which follow are caused by re-entry of the excitation wave. These investigators, who induced ventricular fibrillation in dogs by the application of a single strong induction shock to the ventricle late in systole, recognize four stages in the development of fibrillation. In the *first* or *undulatory stage*, which lasts for only a second or two, the contractions are rapidly repeated but do not follow the same course over the surface of the ventricle; the electrocardiographic deflections show considerable variability in form. In the *second* stage of *convulsive inco-ordination*, which lasts for from 15 to 40 seconds, the contractions are more frequent and involve smaller areas of the ventricular muscle. The contractions of different areas of the muscle are out of phase so that the ventricle appears to be pulled about convulsively. The *third* stage of *tremulous inco-ordination* lasts for 2 or 3 minutes, the surface of the muscle is broken up into independently contracting areas of ever-decreasing size which are out of phase with one another. Thus, a tremulous appearance is given to the ventricles. The *final* stage of *atonic fibrillation* develops when the developing anoxia of the cardiac muscle causes weakening of its contractile force. This stage appears usually within from 2 to 5 minutes following the first stage and is marked by weak contractions or wavelets which travel only a short distance over the ventricular surface. It ends in complete cessation of all activity.

Ventricular fibrillation in man may result from:—

- a) Electric Shocks—electrocution, lightning stroke.
- b) Chloroform or cyclopropane anesthesia.
- c) Coronary occlusion and other causes of severe anoxia.
- d) Trauma to heart or chest wall.
- e) Ventricular paroxysmal tachycardia, in which fibrillation may be a terminal event.
- f) Toxic doses of digitalis or quinidine.
- g) Various diseases during the death agony.

Ventricular fibrillation, though usually fatal is not

invariably so, for rare instances have been reported in which the ventricles after fibrillating for a brief period resumed their normal rate and recovery occurred. Two methods, chemical and electrical, have been used in attempts to restore the normal rhythm to the fibrillating ventricles. Hooker has shown the efficacy of an excess of potassium in stopping fibrillation and of calcium in restoring the normal beat in the hearts of dogs subjected to electric shock. A 0.5 per cent solution of KCl is injected under pressure into the carotid toward the heart, so that it reaches the coronary system. This stops the heart. When a 0.023 solution of CaCl_2 is then introduced by the same route, the normal cardiac rhythm, in a successful experiment, is restored. Hooker and his associates showed that defibrillation of the dog's heart can be accomplished and the normal beat restored if a countershock, consisting of an alternating current of about one ampere is passed through the heart. In fibrillation due to anoxia (e.g. caused by coronary occlusion) the heart may be defibrillated by either of these two means but the heart muscle is usually unable to develop a forceful contraction owing to the oxygen lack. Wiggers has modified Hooker's procedure by sending into the heart a series of shocks (3-7) of about one second duration and one or two seconds apart. He recommends that when fibrillation follows coronary occlusion cardiac massage should be practiced while the countershocks are being given, in order to increase the blood flow to the ventricular muscle. In fibrillation due to electrocution or other cause, the countershocks may be applied through the chest wall although much stronger currents (20-30 amperes) will be required. It is obvious, however, that any method devised for the resuscitation of the fibrillating human heart has little practical application on account of the short time which the heart survives, even though the necessary equipment were on the spot.

THE UNDERLYING PROCESSES CONCERNED IN THE PRODUCTION OF FLUTTER AND FIBRILLATION. CIRCUS MOVEMENT. The observation that flutter and fibrillation could be induced in animals by electrical stimulation of the auricle has led to a much clearer understanding of the nature of these disorders in the human subject.

The three conditions, namely, pure and impure flutter and auricular fibrillation, are believed to be due to a disturbance of impulse initiation and transmission which is of fundamentally the same nature in all three, but varies in degree in each. Pure flutter represents a less advanced stage of the disturbance which in its highest degree leads to fibrillation. Impure flutter is a connecting link between the two. Evidence has been obtained by Mines, by Garrey and by Lewis and his associates that these clinical conditions are due to a *circus movement* of the excitation wave. That is to say, the wave starting at one place takes a devious course through the cardiac musculature to reach the point from which it started and re-enter the path which it had previously traversed. The conception of a circus movement of the excitation wave being the cause of flutter

and fibrillation and an understanding of the factors concerned in the production of the movement dates, however, from the work of Mayer. Mayer induced a circus movement in the umbrella of the jelly-fish (Medusa) by creating a local block and applying a stimulus to one side of the blocked region (fig. 89, I, A). The contraction wave which resulted was forced as a result of the block to take a unidirectional course, and after completing the circuit of the disc of tissue returned to the region of the block, which by this time had disappeared. If the tissue from which the wave had been initiated was again excitable, i.e., had passed from the refractory state, the wave circled the ring a second time, then a third time, and so on repeatedly. When, on the other hand, the disc was stimulated in the absence of a block, a contraction wave set out in both directions and the two waves meeting, after having completed half the circumference of the strip, were suppressed at B (fig. 89, II). That is, further progress of the waves was arrested, for each came to a region of tissue which, being occupied by the other wave, was refractory.

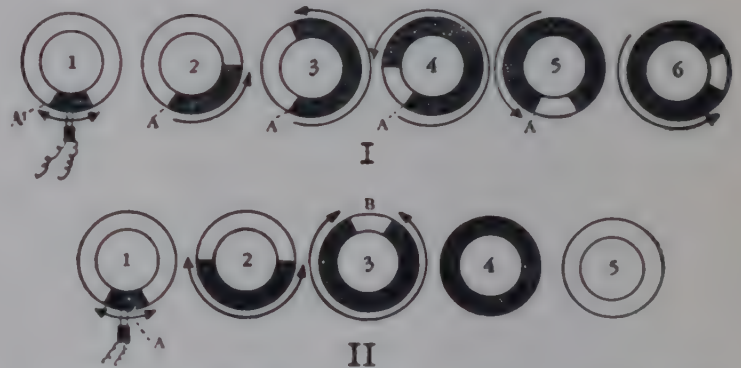


FIG. 89. (Modified from Lewis.) Black = contraction wave. Description in text.

Up to this time fibrillation had been believed to be due either (1) to increased excitability of the cardiac musculature which resulted in the suppression of the normal "coordinating mechanism," the fibers contracting independently of one another rather than as an integrated whole (MacWilliam), or (2) to the initiation of multiple discrete impulses scattered throughout the auricular musculature. It has been shown, however, that areas of depressed excitability—*local blocks*—as first suggested by Porter, constitute an essential factor in the production of fibrillation, rather than heightened excitability. Garrey and Mines linked up Mayer's observations upon Medusa with the fibrillation of cardiac muscle. Mines showed that a similar circular motion of the contraction wave could be induced in the cold-blooded heart. Muscular rings cut from the auricles of large rays were employed. Garrey showed that the conception of multiple foci of impulse initiation scattered throughout the muscle was wrong. He found that if a small piece was cut from the fibrillating muscle, the severed piece of tissue at once ceased to fibrillate, though it still remained excitable and capable of contracting when stimulated. If a series of pieces were cut from the main fibrillating mass the latter became

quiescent when it was reduced sufficiently in size. This observer also induced a circulating contraction wave in large ring-shaped strips of muscle cut from turtle's ventricles. He failed to produce a circus movement if the strips were of small diameter.

From these researches it was concluded that four conditions were involved in the establishment of the circus movement:

- (1) Local blocks
- (2) Shortened refractory period
- (3) Slow rate of conduction of the wave
- (4) An annular course of sufficiently large diameter.

A wave having, as a result of local blocks, been deflected into a circular course can continue to cover the same ground over and over again only if a *gap of responsive (non-refractory) tissue exists between the advancing margin (or crest) of the wave and its tail*. As in the experiments of Mayer cited above, a zone of refractory tissue in front of the wave at once arrests its progress. The shorter the refractory period, the slower the transmission rate, or the larger the circular path, the wider will be the gap. So long as the gap is maintained, i.e., so long as the advance and the retreat of the wave proceed at equal rates and the length of the strip remains unchanged, the movement will continue indefinitely. Closure of the gap by altering one or other of the foregoing conditions brings the circus movement to an end.

Flutter or fibrillation can be induced in dogs by stimulating the auricle with electric shocks repeated in rapid succession (usually around 400 per minute for the production of flutter and about 3000 per minute for the production of fibrillation). During the application of the stimulus the auricular muscle responds at a rate corresponding to the frequency of the shocks, and in a successful experiment continues to beat at an abnormally rapid rate after the stimulus has been withdrawn. But the very high rate of beating—1000 to 3000 per minute—is not maintained as an after effect; the rate drops to around 500 or 600 per minute. The direction taken by the excitation wave, during flutter or fibrillation produced in this way, is quite independent of the point to which the stimulus was applied.

Lewis has studied the mechanism in the mammalian auricle during flutter or fibrillation induced by electric stimulation and has come to the conclusion that multiple blocks are created throughout the auricular muscle. According to him the blocks are produced by the *partial refractory state* of the muscle. This (which should not be confused with the relative refractory period) is defined as the state immediately following the passage of the impulse when some fibers are still refractory while others in the immediate neighborhood have recovered from the previous contraction, and are, in consequence, able to respond to the next impulse. When for any reason the heart rate is greatly increased, diastole is shortened to such an extent that the impulses reach the auricular muscle during this critical period of partial refractoriness. Since, of course, the excitation wave can be transmitted only by the responsive fibers,

it is deflected from its normal course and forced to follow a more devious path. It weaves its way sinuously through the muscle, its transmission time from point to point in the auricle being thereby considerably delayed. The conductivity of the responsive fibers is not impaired, but the longer course which the impulse is compelled to take has the same effect in the production of a circus movement as if an actual depression of

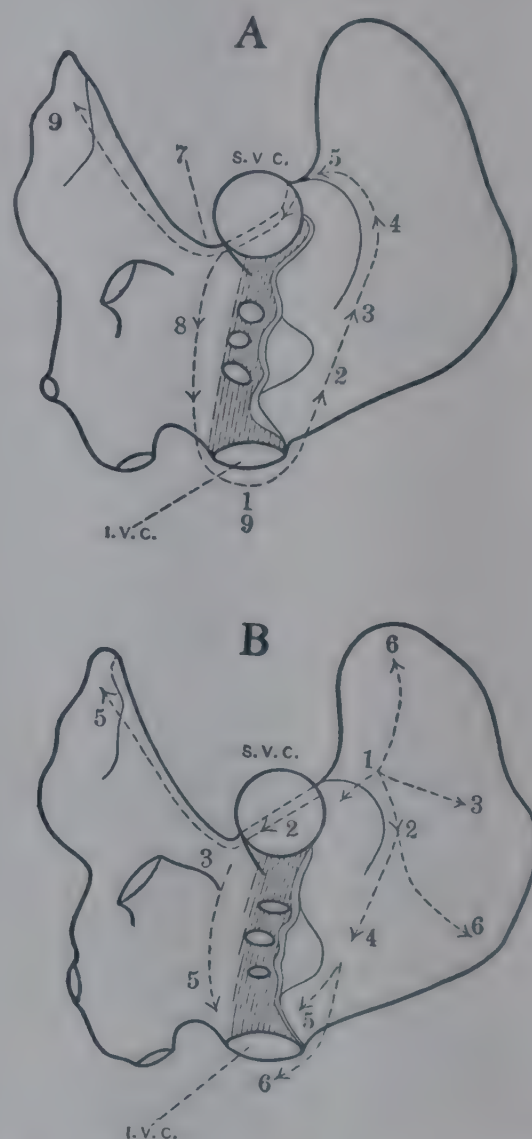


FIG. 90. Diagrams showing, A, circus movement in dog's auricle during flutter, and B, normal direction taken by the impulse; S.V.C., superior vena cava; I.V.C., inferior vena cava. The values written on the diagrams are the relative times in seconds at which the excitation was found to reach the points marked by arrow heads. The direction of each arrow head indicates the ascertained general direction taken by the excitation wave in passing that particular point. (After Lewis.)

conductivity existed. The lengthening of the transmission time combined with the shortening of the refractory period of the muscle, which automatically supervenes when the cardiac rate becomes very rapid, permits the impulse to continue its circular course upon reaching the point from which it started. The final condition, however, must be present, namely, a ring of tissue sufficiently large in diameter to permit a proportion of the fibers to become responsive before the contraction wave again reaches them. On the other hand,

if flutter or fibrillation exists either of the following changes will tend to close the gap between the head and the tail of the revolving wave and bring the circus movement to an end.

- (1) Lengthening of the refractory period.
- (2) Shortening of the transmission time, either by increasing the conductivity of the muscle or through the transference of the excitation wave to a smaller ring of tissue.

THE LOCATION OF THE CIRCULAR PATH TAKEN BY THE IMPULSE. The impulse is believed to travel in those natural rings of muscle encircling the openings of the great veins. Lewis has mapped out the course taken by the excitation wave during experimental flutter; contacts were placed upon the auricular muscle and the times of arrival of the wave at different points recorded. In many instances it was found to travel in the right auricle from below the inferior vena cava, up the taenia terminalis and around the superior vena cava, thus following an annular course which included both caval orifices (fig. 90, A). This route is, of course, quite different from that which the wave normally follows (fig. 90, B). The course taken by the excitation wave is not dependent upon the point of stimulation; it follows the same course whether the auricular muscle is stimulated in the region of the appendix, near the inferior vena cava or elsewhere.

The *circular* (really elliptical) or *mother wave* is the governing factor in the flutter rhythm, from it *centrifugal waves* are thrown off, like sparks from a Catherine wheel, which travel through the auricular musculature and die away in the outlying regions, e.g., right and left appendices and the sleeves of the great veins.

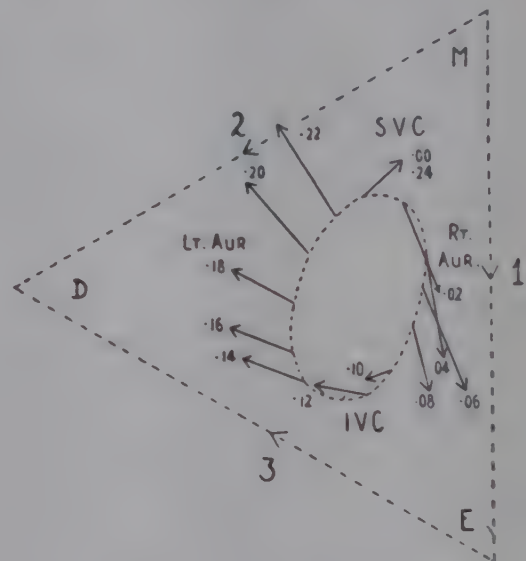
There seems to be little doubt that clinical flutter, like the experimental condition, is due to a circus movement. Further evidence for this view was afforded by a study of the movements of the electrical axis (see p. 184) in patients suffering from the disorder. Simultaneous records were taken from three leads represented as shown in figure 91, by lines joining a point near the manubrium sterni, the ensiform cartilage and the seventh dorsal spine. These form an equilateral triangle embracing the base of the heart. The direction of the electrical axis was determined at $\frac{1}{10}$ second intervals. As shown in the figure the axis was found to rotate anti-clockwise through an angle of 360° .

Flutter and fibrillation are now considered to be essentially the same nature. Impure flutter is a transition stage between pure flutter and auricular fibrillation in nature. In pure flutter the central or mother wave is repeated over and over again with precise accuracy. It and the centrifugal waves pursue their prescribed courses uniformly from cycle to cycle. In impure flutter the irregularity is accounted for by the greater degree of deflection of the centrifugal waves. This is brought about supposedly through an increase in the partial refractory state, i.e., more unresponsive fibers are thrown in the path of the waves in their passage through the eccentric regions of the musculature; it

is to be expected that when waves are forced to pick a very devious way through the muscle their course will not be repeated faithfully from cycle to cycle. The path of the central wave is thought, however, to be disturbed relatively little.

In fibrillation, though the general revolving movement of the mother wave is still maintained it is not believed to follow precisely the same course from cycle to cycle as it does in flutter.

The theory of circus movement as outlined is very widely though not universally accepted. Brams and Katz believe that if a circus movement is responsible for flutter and fibrillation more than one circulating wave must exist. They base this conclusion upon the



fects will tend to close the gap and slow the auricular rate. (3) It slows conduction through the junctional tissue. The vagal effect (1) is therefore opposed to the direct effect upon the auricular muscle. (2) The former usually overbalances the latter, with the consequence that when the drug is given in auricular fibrillation the auricular rate is slightly increased. By slowing A-V conduction (3), however, the drug serves to block impulses passing to the ventricle, and so permits fewer impulses from the auricle to reach the lower chambers. The ventricular rate is therefore slowed and rendered more regular. When given in flutter the drug brings on auricular fibrillation. This effect is probably due to the vagal effect of the drug in increasing the transmission rate, and so of speeding up the revolutions of the wave. When the drug is discontinued the fibrillation frequently ceases, to be replaced by the normal rhythm. This action of the drug is made use of in the treatment of flutter; the conversion of the latter into fibrillation is aimed at deliberately. Digitalis, according to Gold and Cattell also acts directly upon the ventricular muscle fibers in heart failure, increasing the force of contraction.

QUINIDINE (an isomer of quinine) also exerts a three-fold action in fibrillation. (1) It depresses or abolishes vagal tone and so lengthens the refractory period of the auricular muscle and decreases the transmission rate. This action upon the vagus is therefore opposite to that of digitalis. (2) It acts directly upon the auricular and ventricular muscle, lengthening the refractory period (by from 50 to 100 per cent) and slowing the transmission rate. (3) It depresses conduction in the junctional tissues. Its action upon the junctional tissue will, like digitalis, protect the ventricle from the rapid rhythm of the auricle. The lengthening of the refractory period of the auricular muscle tends to close the gap between the crest and tail of the circulating wave and so to bring the circus movement to an end. The prolongation of the transmission rate will, of course, have the opposite effect namely, to widen the gap, but the former action usually prevails and the circus movement is abolished, the normal auricular rhythm being restored in about 60 per cent of cases of auricular fibrillation. When the refractory period and the transmission rate are lengthened equally the circus movement obviously will persist (gap not changed) but the auricular rate is reduced (the wave revolves more slowly). Quinidine thus differs in action from digitalis which does not abolish the fibrillation of the auricle or reduce its rate of beating. In the restoration of the normal auricular rhythm by quinidine fibrillation is frequently converted first to flutter.

The different effects of quinidine upon the heart interact in a complicated manner. For example, its action upon the ventricular rate will be the resultant of the following three effects.

(1) Rapid auricular beating tends automatically to depress conduction through the A-V connections. Therefore when the rate of the auricle is reduced by the drug, A-V conduction is increased.

(2) The reduction in vagal tone also increases A-V conduction.

(3) The direct effect of the drug upon A-V conduction, as stated above, is one of depression.

As a matter of fact (1) and (2) frequently overbalance the last effect (3) and some increase in the ventricular rate results.

Quinidine in overdosage produces severe toxic effects among which are auriculo-ventricular block, extrasystoles, paroxysmal tachycardia, and even death as a result of ventricular fibrillation. This latter effect of the drug, it has been suggested, is due to its setting up a circus movement in the ventricle, as a result of its greater effect in reducing the rate of conduction in the ventricular muscle than in lengthening the refractory period. The return of the normal auricular contractions under quinidine treatment is sometimes, though rarely, followed by the dislocation of an intra-auricular thrombus and death from embolism. Complete standstill of the heart has also been reported as a result of the

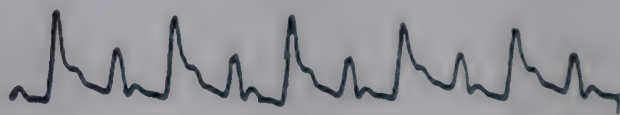


FIG. 92. Radial tracing showing pulsus alternans (after Mackenzie).

paralysis by the drug of the sino-auricular and auriculo-ventricular nodes and other tissues capable of impulse initiation.

C. ALTERNATION OF THE HEART. PULSUS ALTERNANS

This is a condition in which every second wave in a pulse tracing is of relatively small amplitude. This peculiarity of the arterial pulse is due to alternate variations in the strength of the ventricular systoles, and to a smaller quantity of blood being ejected into the aorta during the weaker beat. Figure 92 shows a typical sphygmogram of this condition. There is as a rule little or no difference in the lengths of the intervals between pulse beats. When a slight difference does exist, the interval succeeding the strong beat is then longer than that following the weak beat. It will be remembered that in the bigeminal pulse, which might in some instances be confused with alternation, there is inequality in cycle lengths (p. 196), but the longer interval follows the *weak* (premature) beat. Furthermore, in alternation the

ventricular rhythm does not share, or does so very rarely, in any irregularity of the pulse intervals which may occur in the arterial tracing. The electrocardiogram, for instance, shows no discrepancies in the length of the intervals between the R waves. The slight variations in the pulse intervals are attributed by Lewis to a slower rate of transmission of the weaker pulses to the periphery. When records are taken simultaneously of the apex and the arterial pulse, it is sometimes found that the weak beats of the former coincide with the strong beats of the latter. This discordance between apex and arterial beats is explained

alternation may occur without alternation of the pulse.

It is not possible to detect *pulsus alternans* by palpation of the pulse, the variations in strength of the pulse beat being too slight to be perceptible, but it is clearly revealed in the sphygmogram (fig. 92). It may also be detected by means of a blood pressure armlet. The pressure in the armlet is raised gradually, when it is found that at a certain level the weaker beats are suppressed, but the stronger beats get through. The pulse at the wrist is then precisely half the ordinary rate. The pressure during the weaker beats may be as much

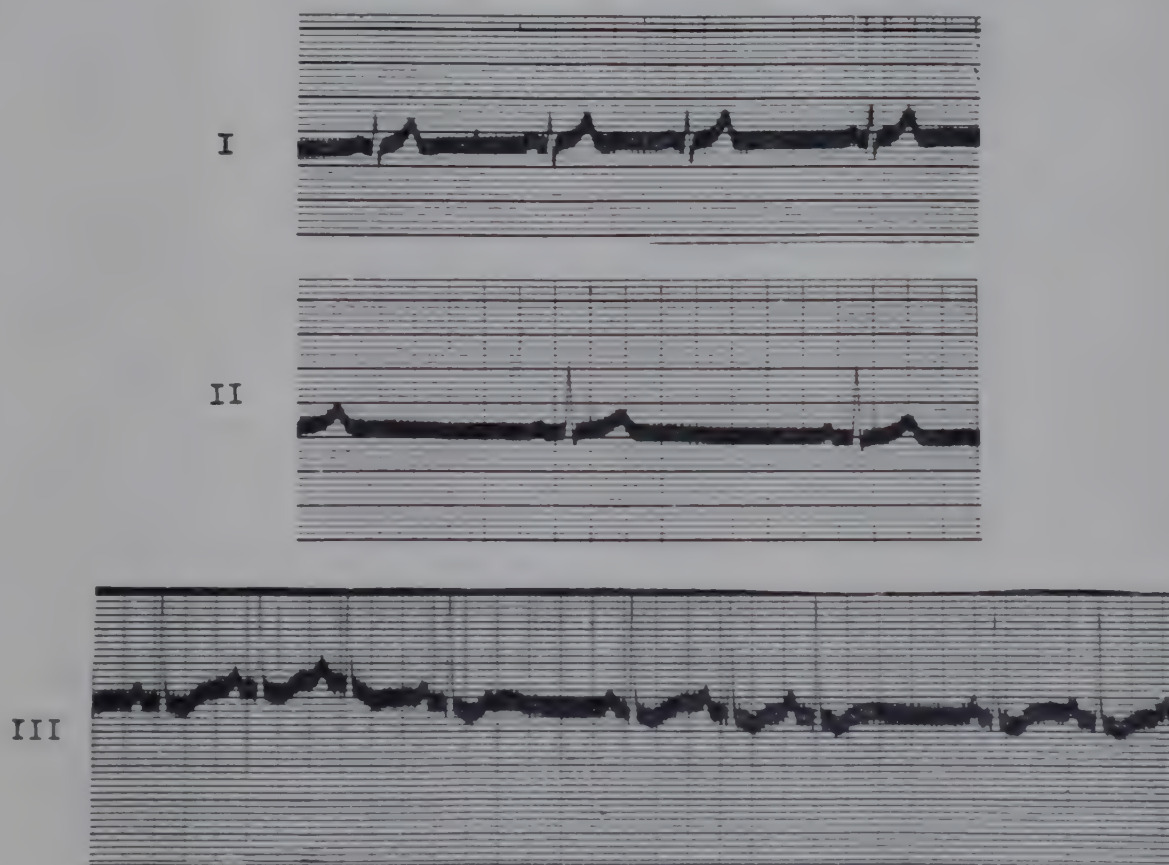


FIG. 93. I, sinus arrhythmia; II, sinus bradycardia; III, sino-auricular block. (Kindness of Dr. John Hepburn.)

upon the assumption that those muscle fibers which contract during the weak apical impulses though less numerous are actually more effective in ejecting the blood than those causing the stronger thrusts at the apex. (See, Theory of Alternation, below.) The appearance of alternation in the electrocardiogram (e.g., alternate variations in the height of the R wave) is rare. When this so-called *electrical alternation* does occur the larger deflections sometimes correspond to the weaker pulse beats. But, it will be recalled in this connection that the deflections of the electrocardiogram are determined by the balance of the electrical forces developed during the cardiac contraction rather than upon their total value. Electrical

as 25 mm. Hg below that during the stronger, but usually the pressure difference is not more than 5 or 10 mm. Persistent alternation of the heart when the pulse is slow or of normal frequency is usually indicative of grave disease of the myocardium. Alternation sometimes also occurs at rapid rates of beating, e.g., auricular fibrillation, paroxysmal tachycardia etc., but it is then of less serious significance.

THEORY OF ALTERNATION. The "all or none" law states that the cardiac muscle responds maximally to any stimulus that is capable at all of evoking a response. It is apparently difficult to reconcile this principle with the varying force of the ventricular contractions in alternation, unless it be assumed that during the weak

beat, a smaller proportion of the heart fibers respond than during the strong beat. This is the prevailing view.

The heart, it is thought, must be in what has been called a *hypodynamic* state in order for alternation to occur. That is, the heart muscle is so depressed that only half of its fibers have recovered from the previous contraction before the impulse arrives. These fibers alone contract, and when the next impulse arrives they are still refractory, but those which had not previously contracted have recovered their irritability and now respond. In this condition all beats are weak but equal. Should a ventricular extrasystole occur in such a heart, the long pause which follows shifts the balance between the refractory and the non-refractory fibers and precipitates the alternating rhythm. After the long pause of the premature beat a larger proportion of fibers have had time to recover and are therefore able to respond to the impulse. The next impulse, however, finds the muscle in a partial refractory state, i.e., only a small proportion of the fibers have by this time recovered. They only can respond—a weak beat results. This small proportion of fibers when the next impulse arrives will in turn be refractory, but the larger proportion which had not previously contracted will now respond—a strong beat results. So the alternating rhythm is perpetuated, the fibers which responded during one contraction fail to contract at the next beat and conversely those which had failed to respond to one impulse respond to the next.

D. IRREGULARITIES DUE TO VARIATIONS IN VAGAL TONE

1. SINUS ARRHYTHMIA (fig. 93, I)

This is a condition in which rhythmical variations in the rate of the whole heart occur synchronously with respiration. It is due to alterations in the strength of the vagal influence upon the pacemaker (S-A node) as

a result of the respiratory excursions, the heart rate increasing toward the end of inspiration and slowing toward the end of expiration. It is a youthful irregularity, being very common in children, and may be considered a physiological phenomenon. That it is entirely of vagal origin is shown by the fact that it is abolished by atropine. It also disappears when the heart rate increases as a result of exercise, fever, etc., but is enhanced by deep breathing.

II. PHASIC IRREGULARITY

In this disorder periodic slowing of the heart occurs for a few seconds quite independently of the respirations. It also is a vagal effect since it is abolished by atropine. The manner of its production is unknown. It occurs in convalescence from acute fevers, and sometimes during the administration of digitalis.

III. SINUS BRADYCARDIA (fig. 93, II)

This is a persistent slowing of the whole heart due to increased vagal tone influencing the sino-auricular node. The rate may be as slow as 40 per minute. Bradycardia of this nature occurs in apparently healthy persons, many of whom are athletes.

IV. SINO-AURICULAR BLOCK (fig. 93, III)

The entire heart (auricles and ventricles) misses a beat at regular or irregular intervals. The condition thus differs from A-V block in which only the ventricle misses (p. 190). A complete set of waves is therefore dropped from the venous or electrocardiographic tracing, and the arterial pulse intermits. Since the condition is temporarily abolished by atropine and may be induced by stimulation of the vagus, it is probable that the missed beats are due to the action of the nerve upon the S-A node. Sino-auricular block sometimes results from digitalis administration.

CHAPTER XXV

THE REGULATION OF THE HEART'S ACTION

THE HEART RATE

In general, the rate of the heart bears an inverse relationship to the size of the animal, and a direct relationship to the metabolic rate. The heart rate in the canary, for example, is in the neighborhood of 1000 beats per minute, whereas that of the elephant is about 25. The average rate in adult man is around 70 per minute, but there is a rather wide variation between individuals, a rate considerably below or above this average being not uncommon. Muscular training tends to reduce the cardiac rate; athletes not infrequently having a pulse rate between 50 and 60. On the other hand, a rate between 80 and 90 is sometimes seen in other healthy persons. The rate diminishes progressively from birth, when it is around 130 per minute, to adolescence, but increases slightly again in old age. Among physiological conditions which temporarily increase the heart rate are, *muscular exercise* (p. 210), *emotional excitement* and *high environmental temperature*. It also increases during *digestion*. The rate is lowered during *sleep* (55 to 60). Among pathological conditions which cause an increase in cardiac rate are *hemorrhage*, *surgical shock*, *hyperthyroidism*, *fever* and certain *cardiac arrhythmias*, e.g., paroxysmal tachycardia (p. 196), auricular fibrillation, etc.

Tachycardia and *bradycardia* are general terms used to denote, respectively, any considerable increase in heart rate above, or reduction below, the normal average.

Cardiac behavior is influenced by three agencies, I, *nerves*, II, *chemical materials*,—hormones, metabolites and inorganic salts in the blood. III, *mechanical effects* exerted upon the muscle fiber itself by the blood within the heart chambers. Each of these will be considered separately.

I. NERVOUS CONTROL OF THE HEART

The heart, as we know, beats rhythmically after its complete separation from the central nervous system (p. 156) but in the intact animal this automatic action is under the continuous influence of nervous impulses. The nervous mechanism comprises groups of nerve cells in the medulla—the *cardiac centers*; various *afferent pathways* along which impulses are conveyed to

these centers from numerous regions of the body; and the *vagus* and *accelerator* or *augmentor* nerves which transmit impulses from the centers to the heart.

THE VAGUS NERVES

The vagus nerves are cardio-inhibitory. This action was discovered by the Weber brothers in 1845. They convey fibers, belonging to the parasympathetic division of the involuntary nervous system, from a center in the medulla (*cardio-inhibitory center*) to the special tissues of the heart. The medullary center was located by Miller and Bowman in the dorsal nucleus of the vagus situated in the floor of the 4th ventricle. Weak electrical stimulation of this area produced slowing of the beat, and stronger currents complete arrest of the heart. The cardiac fibers of the vagus separate from the trunk of the nerve in the neck between the origins of its superior and inferior laryngeal branches. Intermingling with fibers of the accelerator nerves they enter into the formation of the deep and superficial cardiac plexuses whence they are continued to the heart.

Fibers derived from the *right nerve* terminate around ganglion cells in auricular tissue in the immediate neighborhood of the sino-auricular node (p. 163). These cells serve as relay stations in the transmission of the vagal influence; their axons enter the node and are disposed in a plexiform manner around groups of muscle cells in the nodal tissues. The *left nerve* establishes similar relationships with the auriculo-ventricular node. Its terminations arborize around ganglion cells in the interauricular septum which in turn send axons to the muscular elements of the nodal tissue. The connections of the two nerves are not, however, confined to the respective nodes, for though the right nerve is chiefly distributed to the sino-auricular and the left to the auriculo-ventricular node, each node also receives some filaments from the opposite nerve.

Stimulation of the cardiac vagus causes pronounced slowing or complete stoppage of the heart and, in consequence, a fall in blood pressure (fig. 94). The slowing is brought about mainly through the lengthening of diastole, the duration of systole being relatively little affected. When the heart

ceases to beat it does so in the diastolic phase of the cycle, appearing fully relaxed and engorged with blood. For these reasons the vagi are sometimes referred to as the diastolic nerves. The vagal effect upon the heart thus resembles the action of an excess of potassium (potassium inhibition, p. 158).

When complete stoppage of the heart is caused by vagal excitation the ventricles, but usually not the auricles, commence after a time to beat again, though the stimulation of the nerve is continued. This is spoken of as the "*escape of the heart*" from the inhibitory influence. The amplitude of the returning contractions is frequently greater than usual. The escape phenomenon cannot be explained with entire satisfaction; it is not due simply to fatigue of the nerve and its failure to transmit impulses. The distension of the cardiac

order to evoke a response from the auricle a stronger stimulus must be applied to the muscle during vagal stimulation than at other times. The slowing, or stoppage of the ventricular beat is an indirect effect due to auricular slowing, or arrest of the auricular contractions; or to depression of conduction in the auriculo-ventricular connections. That is, in the latter instance, partial or complete heart block is temporarily induced. If the A-V bundle is severed vagal stimulation is then without effect upon the ventricular rate.

The effect of vagal stimulation upon the auricular rate is ascribed by Eyster and Meek to a shift of the pacemaker to a less rhythmical region, that is, to the production of a block in the upper part of the S-A node, or, with stronger stimulation, to complete suppression of impulse formation in this region. The duty of initiating the impulses devolves then upon regions, e.g., the lower part of the S-A node, the A-V node, or other parts of the special tissues possessing lower rhythmical powers. Evidence for this view is afforded by the observation that shortening of A-V intervals or the development of nodal rhythm (see p. 194) may result from vagal stimulation. It has also been shown that primary negativity can no longer be located in the upper part of the sino-auricular node (p. 163) when the vagus (right) is strongly stimulated but is found to have descended to the lower part of the S-A node or to the A-V node. Potassium salts also cause a shift of the region of primary negativity from the upper to the lower part of the S-A node—another example of the similarity between vagal and potassium inhibition. Potassium also depresses auriculo-ventricular conduction.

The right and left vagus nerves differ in their effects. Stimulation of the right nerve which, as already mentioned, terminates chiefly in the S-A node, results mainly in slowing and weakening of the auricular beat, and, as a secondary result of this, in reduction of the ventricular rate. Excitation of the left nerve which ends chiefly in the A-V node causes ventricular slowing or stoppage, by depressing A-V conduction and blocking the auricular impulses; little effect upon the auricular rate results. An electrocardiogram, for example, taken during stimulation of the left nerve shows a greater number of P (auricular) than of R (ventricular) deflections.

The difference between the effects of the two nerves varies considerably in different species. For example, the left nerve in the tortoise depresses conduction from

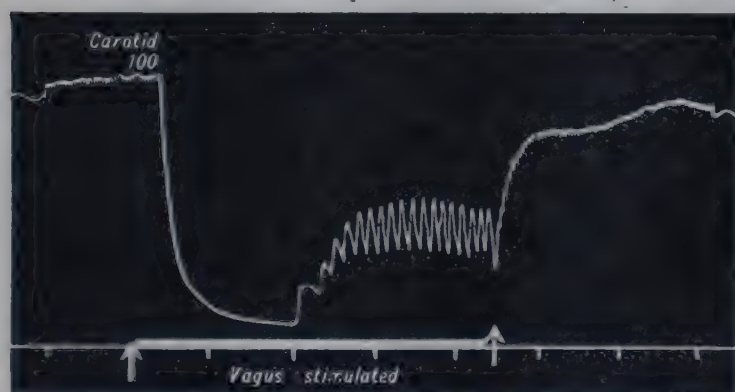


FIG. 94. Showing the effect of vagal stimulation upon the arterial blood pressure. Note that although stimulation was continued, escape occurred, which in this instance was confined to the ventricles (McDowall).

chambers (lengthening of muscle fibers, p. 216) by the blood accumulated during the period of cardiac quiescence is probably a factor. There is some evidence that acceleration of acetylcholine destruction is concerned in the escape mechanism. Nahum and Hoff found that the escape phenomenon is greatly diminished after adrenalectomy and excision of the stellate ganglia, and conclude that adrenaline and the sympathetic nerves play an essential rôle in its production. The impulses which re-start the heart apparently arise from some level in the junctional tissue below the level of the S-A node.

In mammals the vagus nerves exert their effects upon the heart through their action upon the auricular muscle and the junctional tissues. They exert no direct action upon the ventricular muscle. The auricular effects are, *slowing* and *strengthening* of the beat, and *shortening of the refractory period*. *Irritability* of the muscle is also depressed, i.e., in

auricle to ventricle but exerts no effect upon the auricular rate, while slowing of the auricular rate is the sole result following stimulation of the nerve of the right side. In the dog similar differences have been demonstrated. Nevertheless, in the latter animal and in other mammals the right nerve depresses conduction to a greater degree than has been supposed, its effect being merely masked by the greater effect which this nerve, as compared with that of the left side, exerts upon the auricular rate. Increase in heart rate automatically depresses A-V conduction; consequently when the right nerve is stimulated the slower rate which results induces an improvement in conduction which will offset any direct depressing effect of this nerve upon the A-V tissues. Lewis and Cohn found that when arrangements were made to maintain the auricular rate constant during stimulation of the right vagus, the effect upon conduction was only slightly less than that shown by the left nerve.

When the auricular beat is abnormally rapid as a result of a circus movement (p. 201) vagal stimulation increases the rate at which the impulse is transmitted through the auricle. This effect, however, is not the result of any favorable influence which the nerve exerts upon the fundamental property of muscle-fiber conduction, but is due rather to the shortening of auricular systole and, in consequence, of the refractory period of the muscle. The state of partial refractoriness which the rapid beating had induced is lessened. This enables the impulse to take a shorter course which in turn causes a still more rapid fibrillating rate (up to 3000 per minute). This effect of stimulation of the vagus in the conditions of flutter and fibrillation has been termed *rapid re-excitation*. The phenomenon is demonstrable in experimental flutter either by direct stimulation of the nerve or by the administration of a vagotropic drug such as pilocarpine. It is possible that it occurs occasionally as a temporary manifestation in clinical flutter or fibrillation. The effect of vagal stimulation upon the A-V connections during flutter or fibrillation is, as in the normal heart, to depress conduction and slow the ventricular rate.

The tone of the vagus

During the normal life of the animal the vagus nerves exert a continuous restraint upon the action of the heart. In other words, the vagus or rather, the cardio-inhibitory center, possesses tone, impulses passing from it in a continuous stream to the heart. This effect, which may be compared to the action of a dragging brake, can be readily demonstrated in animals by cutting or freezing the nerves. The heart's action then immediately becomes greatly accelerated. The increase in rate following the removal of the vagal influence also occurs though the stellate ganglia (p. 938) have been previously excised; the result therefore

cannot be due to an increased action of the accelerator nerves. The tonic action of the vagus nerves may be annulled by means of atropine, $\frac{1}{16}$ to $\frac{1}{8}$ grain being required in man to completely abolish their effects, the heart rate then increasing to 150 or 180 per minute. The difference between this rate and the normal resting rate of 70 per minute, therefore, represents the vagal effect which is being constantly exerted under ordinary circumstances. Various conditions, physiological and pathological, alter the tone of the vagus center. The tone is naturally higher in some species, e.g., the dog, which is capable of feats of endurance, than in others, e.g., the domestic rabbit. It also shows individual variations in man, athletes usually showing a higher tone than those who lead sedentary lives.

Vagal tone is apparently reflex in nature and dependent upon afferent impulses flowing to the vagus center especially along the sinus and aortic nerves (p. 241, 242). Section of these nerves causes an increase in heart rate and little further acceleration occurs as a rule when the vagi themselves are subsequently severed.

THE ACCELERATOR OR AUGMENTOR NERVES

The accelerator fibers were described by Von Bezold in 1863. They belong to the thoracolumbar division of the involuntary nervous system and arise from cells situated in the lateral horns of the upper thoracic segments of the spinal cord—I to V T (see p. 940). These cells constitute a spinal cardio-accelerator center. The preganglionic fibers enter the gangliated cord of the sympathetic to connect with cells in the *inferior, middle and superior cervical ganglia*. In many animals and also often in the human subject the inferior cervical and the first thoracic ganglia are fused into an irregularly shaped structure called the *stellate ganglion* from which accelerator fibers pass directly to the heart. The heart also receives accelerator fibers *directly* from the sympathetic chain as far down as the 4th or 5th thoracic ganglion. In order, therefore, to remove all accelerator influence from the heart it is necessary, as shown by Cannon, Lewis and Britton, to interrupt these connections as well as to remove the stellate ganglia. The axons of the cells of the cervical ganglia (postganglionic fibers) form the *inferior, middle and superior cardiac nerves* (fig. 95). The post-ganglionic fibers, especially those forming the nerves of the right side, terminate in the sino-auricular node. Those of the left side are

distributed mainly to the AV node and bundle. According to Nonidez, the sympathetic efferent fibers which reach the heart are contained mainly in the middle cardiac nerve. The superior cardiac nerve is distributed to the large arteries while the inferior cardiac nerve is mainly afferent. The spinal accelerator center is subordinate to higher centers. The precise locations of the latter are not known, but the experiments of Beattie, Brow and Long indicate the presence of a center in the posterior hypothalamic region (p. 883); and Green and Hoff observed changes in heart rate, in blood pressure and in limb and kidney volumes upon stimulating the cerebral cortex (motor and

prone, during chloroform anesthesia, to induce fibrillation of the ventricles (p. 198). The increase in the ventricular rate that occurs when these nerves are stimulated is accomplished usually through the shortening of both systolic and diastolic periods, but systole is curtailed to a greater degree than diastole, so that the ratio of the length of systole to the length of the entire cardiac cycle

$\left(\frac{\text{systole}}{\text{cycle length}} \text{ ratio} \right)$ is decreased.

There is evidence that the effect of the accelerators upon A-V conduction is, as one would expect, opposite to that exerted by the vagus.

Accelerator tone

The accelerators also exert a tonic action. This may be demonstrated by excision of the stellate ganglia when the heart rate slows. Gasser and Meek, for example, found that when the ganglia were removed but the vagi left intact an immediate and marked fall in rate (about 40 per cent) occurred; further slowing occurred later which was attributed to a rise in vagal tone. Slowing of the rate is produced, however, by excision of the ganglia, even though vagotomy has been performed previously; this fact of course precludes the possibility of the immediate reduction in rate following excision of the stellate ganglia being due to increased vagal tone.

Bronk and his associates have demonstrated the existence of accelerator tone in the cat by recording the action potentials from nerves leaving the stellate ganglion. A fairly continuous discharge of impulses at a rate of from 5 to 20 per second was observed. Stimulation of the central end of an afferent nerve (e.g., sinus or aortic nerve) caused a discharge of impulses in the efferent fibers at the frequencies of the afferent impulses.

CARDIAC REFLEXES

Under ordinary conditions, the activities of the cardio-inhibitory and cardio-accelerator centers which result in the continuous discharge of impulses along the corresponding cardiac nerves are in turn dependent to a very large extent, if not entirely, upon the reception of impulses by afferent paths. In other words, the maintenance of the tone of the centers, and so of the normal resting rate of the heart, and the alterations in rate which occur under various physiological conditions are in large measure either reflex in nature or due to impulses received from cerebral centers. The impulses which stream into the nervous centers

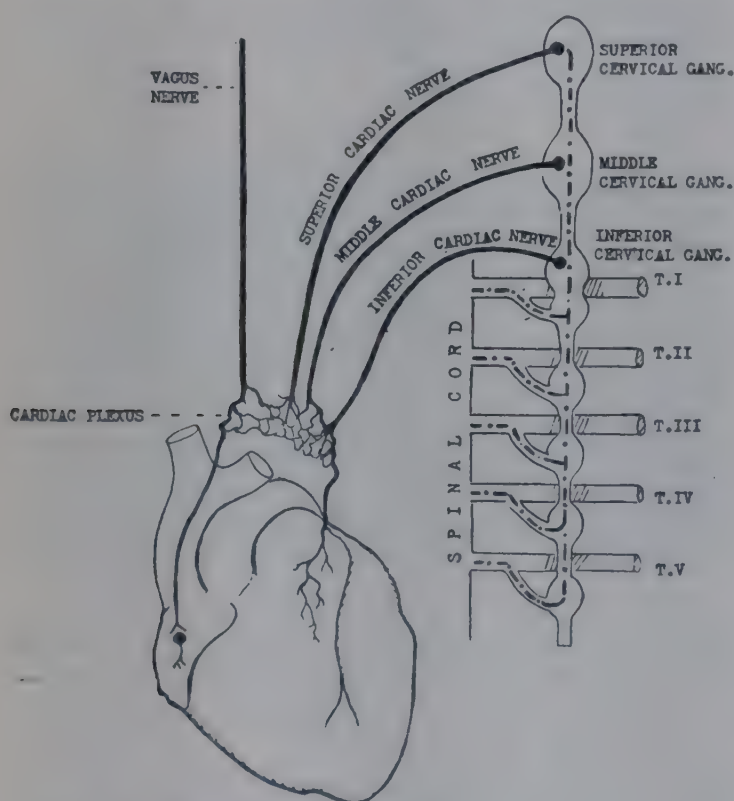


FIG. 95. Diagram of the cardiac nerves. Broken lines = preganglionic sympathetic fibers.

premotor areas) in cats and monkeys. A medullary center also probably exists.

Stimulation of the accelerators causes quickening of the rate of both auricles and ventricles and an increase in the force of the contractions. We have seen that the vagus exerts its influence chiefly upon the auricle and junctional tissue, affecting the activity of the ventricle only indirectly. The accelerator nerves, on the other hand, exert, as well, a direct action upon the ventricular muscle. Stimulation of the accelerator nerves may so excite the ventricles as to induce fibrillation. Fibrillation of the auricles, on the other hand, is not induced by this means. We have also seen that adrenaline (which has an action upon the heart similar to that following stimulation of the accelerators) is particularly

arise in all parts of the body, the heart itself included. By these influences the tone of either center may be exalted or depressed, and corresponding changes produced in the cardiac rate. For example, Goltz showed many years ago that reflex inhibition of the frog's heart could be induced by repeated gentle taps upon the intestines. Reflex slowing of the pulse can usually be demonstrated in the human subject by pressure upon the eyeball at the outer canthus (oculo-cardiac reflex), or by the stimulation of nasal branches of the fifth nerve. Stimulation of afferent fibers in the respiratory passages¹ as by the inhalation of irritating vapors, e.g., anesthetics, is particularly likely to cause reflex inhibition of the heart. Extrasystoles and bradycardia have been demonstrated electrocardiographically in man during abdominal operations, the irregularities being the consequence, apparently, of visceral stimulation. Excitation of the central end of various peripheral nerves, e.g., the sciatic, causes reflex changes in the pulse rate. In these last instances acceleration is more readily obtained than inhibition. The irradiation of impulses on to the cardiac centers from the cerebral centers, e.g., from the motor area at the commencement of muscular exercise (p. 210) or from regions concerned with emotional manifestations, are held responsible for the changes in pulse rate which occur under these conditions.

Afferent endings in the heart and aorta

Afferent fibers are contained in the cardiac vagus itself; the receptors of these lie within the heart tissues, and upon the aortic arch. If, therefore, the cardiac vagus on one side be cut and its central portion (i.e., the end leading to the brain) stimulated, a reflex through the cardio-inhibitory center and the opposite vagus occurs which alters the cardiac rate. The nature of the change in rate—whether acceleration or inhibition—which will result from stimulation of the central end of the vagus or of most other afferent nerves cannot always be foretold. As a general rule, however, stimulation of afferent spinal nerves causes acceleration, and of afferent vagal fibers inhibition. The effect which is obtained depends also to a large extent upon the intensity of the stimulus, strong stimuli being more likely to increase the cardiac rate, weak ones to depress it; it depends

also upon the species, in some animals quickening is more readily obtained than slowing, in others the reverse is true. For this reason it has been thought that the vagus and other nerves contained two types of afferent fiber, each type being responsive to different strengths of stimulation, and each being contained in variable proportions in different nerves as well as in the corresponding nerves of different species.

In some animals the vagus gives off a branch composed entirely of afferent fibers. This nerve terminates in the wall of the aortic arch and in the heart itself. It is known as the *aortic or cardiac depressor nerve* (see p. 241) since when excited it induces cardiac slowing and vasodilatation, and, as a result, a fall in blood pressure.

Marey's law

Marey's law states that the pulse rate is inversely related to the arterial blood pressure—a rise or a fall in pressure causing, respectively, a decrease or an increase in heart rate. These adjustments are subserved by:

- (1) A reflex whose afferent limb is constituted of afferent vagal fibers ending in the aortic arch and heart.
- (2) A reflex in which the *sinus nerve* forms the afferent limb. These mechanisms will be considered in chapter XXVII.

A fall in blood pressure causes an increase in the rate of the heart, however, even after it has been completely denervated; the acceleration is attributed to the liberation of adrenaline.

The Bainbridge reflex

The increase in heart rate induced by a rise in the pressure of blood entering the right auricle is known, after its discoverer, as the Bainbridge reflex. It is carried out presumably through the afferent vagal terminations beneath the endocardium and in the walls of the great veins near their entrance into the auricle. The nerve filaments are stimulated by the increased venous pressure which rises only after the cardiac chambers have been completely filled. Through this mechanism, the heart rate is adjusted automatically to the volume of blood poured into its chambers (the venous inflow).

THE RECIPROCAL ACTIONS OF THE CARDIAC CENTERS

Changes in heart rate are brought about not simply by an increase or a decrease in tone of one or other cardiac center but by reciprocal variations

¹The rabbit's heart is slowed to between 50 and 60 beats per minute by the inhalation of ammonia. By means of this response it is possible to make slowing of the heart a conditioned reflex to the ringing of the bell (see Chapter LXX).

in the tone of both. An increase in heart rate for example is due to a decrease in tone of the cardio-inhibitory center accompanied by an increase in tone of the accelerator center. A decrease in heart rate is the result of increased tone of the cardio-inhibitory center together with reduced tone of the accelerator center. Such a balanced mechanism must make for more rapid, smoother and nicer adjustments of the cardiac rate than would be possible otherwise. Generally speaking, however, changes in tone of the cardio-inhibitory center appear to exert a greater influence than do alterations in accelerator tone. For example, the slowing of the heart which results from a rise in arterial pressure is much less pronounced if impulses from the cardio-inhibitory center have been prevented from reaching the heart by section of the vagi. After removal of the stellate ganglia, on the other hand, the cardiac response to a rise in blood pressure is reduced to a less extent. Also, the increase in cardiac rate which occurs at the commencement of muscular exercise is due to a reduction in vagal tone rather than to an increase in accelerator tone. The reciprocal relationship between the cardiac centers in the reflex acceleration of heart rate resulting from stimulation of the central end of the sciatic nerve has been demonstrated by Hooker and by Bainbridge. Though reduction in vagal tone was the more important factor in the accelerator response, increased tone of the accelerators was also shown. When, for example, the vagi were cut and the heart maintained at a constant rate by stimulation of the peripheral end of one of the cut nerves, or by the administration of pilocarpine, excitation of the central end of the sciatic nerve caused cardiac acceleration. This was attributed to an increase in accelerator tone; adrenaline liberation was not a factor since acceleration occurred after adrenalectomy. More recently, Moore and Cannon have found that after sympathectomy, vagal action is capable of slowing the heart from a rate of 150 beats per minute to 75, and the sympathetic mechanism, after vagotomy, can increase the rate from 125 to 225.

VOLUNTARY ACCELERATION OF THE HEART RATE. Several instances (Taylor and Cameron, and Ogden and Shock) have been reported of individuals possessing the power of voluntarily accelerating the heart rate. In one such case the effect was brought about apparently through the discharge of impulses along accelerator nerves since other sympathetic manifestations, e.g., vasoconstriction, glycosuria and dilatation of the pupils accompanied the increased pulse rate.

THE ACCELERATION OF THE HEART IN MUSCULAR EXERCISE AND IN EMOTIONAL STATES

There are two stages in the cardiac acceleration which accompanies muscular effort, namely, the increase in rate which occurs immediately upon the commencement of the work, and that which develops subsequently and more gradually. The acceleration of the pulse at the outset of the exercise occurs too promptly to be the result of an increased flow of blood from the contracting muscles to the heart (Bainbridge reflex). Miss Buchanan has shown, for example, that with even very light exercise, namely, clenching the fist, the diastolic period *immediately* succeeding the commencement of the movements is shortened. Thus, before the exercise the length of the cardiac cycle was 0.82 second (pulse rate 73). The first cycle after starting the exercise was 0.67 second. Subsequently the cycles shortened progressively to reach a value of 0.56 second; this corresponds to a pulse rate of about 107 per minute. Moreover, it has been shown by other observers that the initial acceleration does not occur if the muscles are moved passively or tetanized by direct stimulation.

The last mentioned observation indicates that the effect is not the result of a reflex elicited through receptors situated in the muscles themselves. It is concluded that the initial acceleration results from impulses arising in the motor areas of the cortex and overflowing on to the cardio-inhibitory center. On the other hand, *if the circulation to the arm or leg is arrested* while the limb muscles are contracting the pulse accelerates and, provided that the limb's circulation remains occluded, the increased rate persists after the exercise has ceased (Alam and Smirk). The effect under such circumstances is evidently due to a reflex from the contracting muscles. Its persistence after cessation of exercise until the circulation is restored and its disappearance thereafter, and also its association with the pain of intermittent claudication (p. 257) strongly suggest that the reflex is initiated from afferent nerve terminals stimulated by metabolites which have accumulated in the contracting muscles. This cardiac reflex, though interesting as a physiological phenomenon is probably of very minor importance in the increased pulse rate in muscular exercise. That depression of vagal tone rather than heightened accelerator tone is the responsible factor is evidenced by the following facts, (a) the shortness of the latent period which is a characteristic of vagal effects, (b) the abbreviation of the cycles through shortening of the diastolic period, which was noted above, is also a criterion of lowered vagal tone (p. 207). Bowen also found that during exercise in man the increase in rate was brought about entirely by short-

ening of diastole. Indeed, systole was actually lengthened at the commencement of the work. Gasser and Meek, experimenting with dogs, found that removal of the stellate ganglia had little or no effect upon the cardiac acceleration occurring early in muscular exercise, whereas this primary increase in rate did not occur after vagotomy. They found, however, that after the initial stages of the work increased accelerator tone contributed as well to the increased frequency. Diastole and systole were both shortened though the vagal effect predominated. The important factor in the delayed effect is no doubt the rise in venous pressure and the elicitation of the Bainbridge reflex (p. 209). Gasser and Meek conclude from their experiments that the chief function of the accelerators is to maintain a steady frequency of the resting pulse and that their influence does not alter to any marked degree under ordinary circumstances, the duty of varying the heart rate devolving chiefly upon the vagal centers. The accelerators provide a factor of safety and, under circumstances of exceptional stress, e.g., strenuous muscular exertion or emotional states, reinforce the vagal effect. The liberation of adrenaline is an additional factor.

It is probable that in such emotional states as fright, anger and mental excitement, the accelerator nerves play a more prominent part in increasing the heart rate than does a reduction in vagal tone. Bond found that sudden startling of an animal, in which adrenaline liberation had been prevented, caused a much greater increase in heart rate if the vagi had been sectioned and the accelerators left intact than in converse experiments (accelerators divided and vagi intact).

THE EFFECT OF DRUGS UPON THE CARDIAC RATE

The efferent vagus pathway, as already mentioned (p. 205), consists of two links—the preganglionic and postganglionic neurons. *Atropine* acts by antagonizing the action of the cholinester which, according to the humoral theory of the transmission of nervous effects, is liberated at the postganglionic terminals. Atropine therefore depresses, or in full doses, completely abolishes vagal action, the effect upon the cardiac rate being the same as if the vagus nerves were cut. *Muscarine*, an alkaloid present in poisonous mushrooms (*Amanita*) has a diametrically opposite effect. Its action upon the cardiac rate imitates that of vagal stimulation, namely, to cause slowing and, finally, complete stoppage of the heart in diastole. The effects of *pilocarpine*, *physostigmine* and the ester of choline, *acetylcholine* (see below) are similar to those of muscarine, causing cardiac slowing or standstill (see also p. 946). Their actions are antagonized by atropine. *Nicotine* first excites the vagus but later acts like atropine, causing vagal paralysis and increased cardiac action. Its site

of action is upon the ganglion cell or at the synapse of the latter with the preganglionic fiber.

THE HUMORAL TRANSMISSION OF VAGAL AND ACCELERATOR EFFECTS

Some few years ago Loewi performed a series of experiments which showed decisively that cardiac inhibition resulting from vagal stimulation is due to the liberation of a chemical substance possessing an action similar to that of *acetylcholine* (see p. 946). It was also shown that the augmentation and increase in heart rate which follow stimulation of the accelerators are due to the action of an *adrenaline-like substance*. His results have been confirmed by others. The experiments were performed as follows. Two frog hearts were perfused with Ringer's solution. One heart (donor heart) was inhibited by vagal stimulation. The perfusion fluid of this heart when perfused through the second heart (recipient heart) caused inhibition of it also. The effect upon the second heart could only have been due to the presence of a chemical material of some sort in the perfusion fluid derived from the first heart; it must have been produced by vagal stimulation. The action of the perfusion fluid upon the recipient heart was annulled by atropine. The cardio-inhibitory action of choline and its ester acetylcholine is also prevented by atropine. The perfusion fluid from a heart during vagal stimulation has been shown, moreover, to cause contraction of the stomach wall of the frog (Brinkman and Van Dam) and of a loop of intestine, effects which are also produced by acetylcholine. The "vagus substance" (Vagusstoff as it was called by Loewi) is also, like acetylcholine, readily destroyed by alkali (or by the esterase mentioned below) but is stable in acid media.¹

The method used by Baingto demonstrate the humoral transmission of vagal effects is shown in figure 96.

It was later demonstrated by Loewi that the heart muscle contained an enzyme—*cholinesterase*—which rapidly hydrolyzed the ester after its liberation into the relatively inactive choline and

¹ Howell was the first to suggest a humoral mechanism underlying the cardio-inhibitory effect. He reported an increase in the concentration of potassium in the fluid perfusing an isolated mammalian heart during vagal stimulation. The resemblance of the action of potassium upon the heart to that produced by stimulation of the vagus has been pointed out on page 206. Howell proposed the theory that the nerve impulses caused the breakdown of some organic compound with the liberation of an inorganic form of potassium (see also p. 949).

acetic acid, and so limited the duration of its action. The action of this esterase is inhibited by physostigmine (eserine). The effect of the latter drug in inhibiting the heart depends solely upon this action. That is, it prevents the hydrolysis of the vagus substance which therefore continues to exert its effect (p. 946).

The liberation of a substance possessing an adrenaline-like action was demonstrated by per-

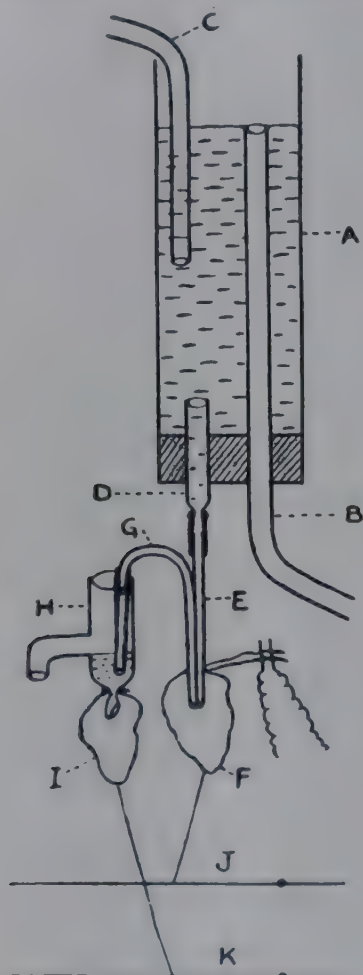


FIG. 96. The perfusion apparatus A is furnished with an overflow tube B, the height of which can be varied to allow alterations in the perfusion pressure. Fluid is delivered through the tube C. The fluid from A passes through the tube D to the inflow limb E of the double cannula which supplies the donor heart F. After irrigating the interior of the donor heart, the fluid passes by the outflow limb G to the glass cannulated tube H to which is attached the recipient heart I. This cannulated tube is provided with a lateral overflow, so that the pressure of the fluid supplied to the recipient heart remains constant. J and K are the levers to which the hearts F and I are respectively attached (Bain).

fusion experiments of a similar nature. Perfusion fluid collected from one heart during stimulation of the accelerator nerves when perfused through a second heart accelerated its rate.

THE SENSORY NERVES OF THE HEART

The ordinary types of stimulus applied to the heart cause no painful sensation.* The exposed

*This fact was first shown by Harvey upon the exposed heart of the Viscount Montgomery (see p. 514).

heart of a conscious human subject, for example, may be stimulated electrically or mechanically without any sensation of pain being experienced. Pathological processes, especially coronary artery thrombosis and angina pectoris, may, on the other hand, give rise to acute and often agonizing pain (p. 280). The results of experiments upon animals and of operations upon man in which the cardiac sympathetic pathways have been interrupted or blocked by means of alcohol injections, indicate that the route for cardiac pain is solely through sympathetic afferents. The pain fibers are contained mainly in the inferior cardiac nerves but some travel in the middle cardiac nerves. The pain impulses then pass through the corresponding cervical ganglia, and the white rami and posterior roots of the upper four or five thoracic nerves (fig. 95, p. 208). Pain fibers also pass from the heart directly (i.e., not through the middle and inferior cardiac nerves) to the upper four or five thoracic ganglia. Pain and stretch receptors have been described in the cardiac muscle.

II. CHEMICAL CONTROL OF THE HEART. THE INFLUENCE EXERTED UPON THE HEART AND VASCULAR MUSCULATURE BY BLOOD-BORNE SUBSTANCES

The known materials in the circulating blood which influence the action of the heart are, (1) the *mineral constituents*—calcium, potassium and sodium; (2) *adrenaline*; (3) *acid metabolites*—carbon dioxide and lactic acid; and (4) *oxygen*. The specific effects of the inorganic constituents upon the perfused heart have already been considered (p. 157). Their proportions in the general blood stream do not vary under physiological conditions, and rarely, if ever, in pathological states to a sufficient extent to affect materially cardiac behavior. Adrenaline has a very definite action upon the heart and vessels which will be considered in Chapter LIX.

Carbon dioxide and lactic acid

Carbon dioxide exerts an effect upon the cardiac and vasomotor centers and directly upon the cardiovascular musculature. Carbon dioxide and lactic acid, formed during the activity of muscle and other tissues, dilate the peripheral vessels (p. 248). The active tissues are thus supplied more generously with blood. In muscular exercise the greater flow of blood through the muscles causes a greater mass movement of blood along the veins and a greater flow into the cardiac

chambers. The higher carbon dioxide tension in the venous blood coming to the heart from the skeletal muscles enhances the extensibility of the cardiac muscle fiber during diastole and, in consequence, exerts a favorable effect upon the filling of the heart. The cardiac output is therefore increased (pp. 215 and 216).

The junctional tissues are particularly sensitive to high tensions of carbon dioxide, auriculo-ventricular conduction becoming markedly depressed when the carbon dioxide excess is such as to cause a fall in pH of the fluids bathing the cardiac muscle fibers. At a pH of around 7.0 complete heart block occurs. A less pronounced increase in CO₂ tension causes slowing of the heart, as a result of depression of the activity of the sino-auricular node as well as of increased tone of the cardio-inhibitory center. The continued exposure of the heart to a high CO₂ tension causes weakening of the beat and the development of irregular rhythms.

An abnormally low tension of carbon dioxide in the blood is sometimes referred to as *acapnia* (Greek; *a*, privative + *kapnos*, smoke). It occurs in conditions associated with increased pulmonary ventilation, the gas being "pumped" or "blown off" from the body in the expired air. The carbon dioxide deficit produces effects which are the reverse of those caused by carbon dioxide excess. Diastole is incomplete, the tone of the capillaries and small veins is increased (p. 250), the venous pressure falls and the heart chambers are insufficiently supplied with blood. The cardiac output, in consequence, is reduced. Diastole becomes shorter and shorter with a consequent rise in cardiac rate; finally, as Henderson and his associates have shown in animals during prolonged artificial respiration with maximum ventilation, the heart enters into a condition of almost continuous contraction. The blood pressure falls and death occurs from circulatory failure.

Low carbon dioxide tension, if accompanied by a change in blood reaction toward the alkaline side, increases the rate of conduction over the auriculo-ventricular bundle. The rate of impulse initiation in the sino-auricular node is increased; the tone of the cardio-inhibitory center is lowered.

Owing to the several factors involved, the effects of carbon dioxide deficit and carbon dioxide excess upon the action of the heart in the human subject offer many difficulties to the investigator. In forced breathing, for example, the respiratory excursions if violent may interfere with the venous return and reduce the cardiac output. Vincent

and Thompson observed a fall in blood pressure during forced breathing which they attributed chiefly to the mechanical effect of the respiratory movements upon the venous return; they assert that the lowered carbon dioxide tension played a minor rôle. If, on the other hand, the respirations are carried out at a different rate and depth the venous return may be augmented and the cardiac output, in consequence, increased. The effect of forced breathing also varies with the subject and with the type of the breathing, thoracic breathing tending to increase the cardiac output, the abdominal type to reduce it. It is not surprising, therefore, that attempts by different workers to determine the effects of alterations in the carbon dioxide tension of the blood upon cardiac action have given conflicting results. Probably the most complete series of experiments relating to this question have been carried out by Grollman, who employed the acetylene method for the determination of the cardiac output (p. 229). He observed a greater output during forced breathing. The increase he attributed to the rise in metabolism incident to the extra work performed by the respiratory muscles, and to the mechanical effect of the respiratory excursions in augmenting the venous return. For, when the forced breathing was carried out with a *carbon dioxide—air mixture* which maintained the carbon dioxide percentage of the alveolar air around the normal value, an increase in the cardiac output occurred of the same magnitude as that occurring when the over-ventilation was carried out with ordinary air. Breathing a carbon dioxide rich mixture caused no change in cardiac output until the carbon dioxide in the inspired air reached about 6 per cent; then a marked increase in the pulmonary ventilation and a rise in the cardiac output occurred. The latter was attributed also simply to increased respiratory activity.

Grollman concludes that carbon dioxide lack must be of an extreme grade before it exerts an effect upon the output of the heart; in ordinary experiments upon the human subject the loss of carbon dioxide falls short of the point where such an effect is produced. In disease, on the other hand, when a profound lowering of the carbon dioxide content of the blood occurs with a consequent change in the pH of the latter toward the alkaline side, deleterious effects upon the circulation and reduction in the cardiac output would be expected to occur as a result of incomplete diastolic filling. In order to prevent the "washing out" of carbon dioxide during artificial respiration Henderson

advocates the addition of carbon dioxide (7 per cent) to the inspired air.

Oxygen

High tensions of oxygen tend to reduce slightly, and very low tensions to increase the output of the heart. In experiments with subjects who breathed mixtures of oxygen and nitrogen in varying proportions, Grollman found that the cardiac output did not alter until the oxygen content of the mixture had been reduced to 11.6 per cent. A moderate increase in the output then occurred. If the oxygen lack is profound or of long duration the cardiac muscle suffers and the output of the heart then, of course, becomes reduced.

Reduction in the oxygen content of the arterial blood by 50 per cent or more causes a diminution in the amplitude of the T wave of the electrocardiogram. This wave may become flattened out or inverted in all three leads if the anoxemia persists. Changes resembling those caused by coronary infarction (p. 281) may make their appearance. These electrocardiographic effects have been observed in disease and in airmen during ascents to over 5,000 feet.

Breathing a mixture with a very high percentage of oxygen slows the *heart rate*. In the early stages of oxygen lack the heart rate is increased. These effects are brought about presumably through the cardiac centers. In the later stages of anoxemia, heart block, extrasystoles and other cardiac irregularities develop and heart failure supervenes. The inability of the heart muscle to contract any considerable oxygen debt has been mentioned (p. 157).

Asphyxia

The combined effects of oxygen lack and carbon dioxide excess upon the heart rate are seen in asphyxia. At first, marked slowing occurs which is largely a secondary effect of the rise in blood pressure (Marey's law, p. 209) induced through the action of carbon dioxide excess and oxygen lack upon the vasomotor center (p. 248). Later, as the strength of the cardiac muscle weakens the blood pressure falls; the heart rate rises and finally cardiac irregularities appear. It has been shown by McDowall that mild asphyxia exerts a delayed effect upon the cardio-inhibitory center. If an animal is asphyxiated for a short time, cardiac slowing occurs after recovery. During the asphyxial period itself slight cardiac acceleration may occur. The delayed effect is considered to be in the nature of an after discharge (p. 814)

of the cardio-inhibitory center. From this observation it is suggested that the mild asphyxia which accompanies muscular exercise may be a factor in the development of the high vagal tone and slow heart rate found in athletes and others who are accustomed to perform heavy muscular work.

III. THE MECHANICAL FACTORS CONCERNED IN THE REGULATION OF CARDIAC ACTION

The effects of mechanical or physical factors, e.g., venous inflow and arterial blood pressure, upon cardiac behavior have been studied in great detail by Starling and his associates. The experiments were carried out upon the heart-lung preparation of the dog. A description of the preparation follows.

The heart-lung preparation

This method enables the output of the left ventricle to be determined at the same time that any one of several factors, e.g., arterial resistance, venous inflow or temperature, is varied as desired, while the remaining factors are rigidly controlled. The following description is taken in the main from Knowlton and Starling's paper (see fig. 97). The chest is opened and artificial respiration instituted. The arteries arising from the aortic arch are ligated, as well as the azygos vein. Cannulae are tied into the innominate artery (C.A.) and the superior vena cava (S.V.C.). The descending aorta is ligated. Blood which has been defibrinated or rendered incoagulable by the addition of heparin is placed in the reservoir F; this is connected by tubing of wide caliber with the cannula in the superior vena cava. The blood is warmed in its passage through a worm immersed in a water bath. The only channel open to the blood from the left heart is through the innominate cannula. The lesser circulation is undisturbed, the blood from the right heart is oxygenated by passing through the lungs to the left auricle. For the sake of simplicity the pulmonary circulation is not shown in the figure. The innominate cannula connects by one limb of a T-tube with a mercurial manometer M¹. The other limb of the T is connected by tubing with a second T-branch, v, the limbs of which are connected respectively with the resistance R, consisting of a rubber finger-stall enclosed in a sealed tube, T, and the inverted test-tube, B. The air in the latter, since it undergoes compression and decompression with the pulsatile variations in arterial pressure, acts like the air cushion in the stand-pipe of a water system, and serves in lieu of the elastic arterial wall (p. 122). The resistance of the flow of blood through R can be raised to any desired height by means of the bulb S and the pressure bottle A. The pressure exerted upon the collapsible finger-stall is measured by the manometer M². The blood after passing through the peripheral resistance collects in the tube N which is provided with a siphon tube Sy. This

total output of the left ventricle remained practically unchanged though the arterial pressure was raised over 100 per cent (table 17).

It is quite evident from table 17 that the heart responded to a greater venous inflow by increasing its output per beat and not by increasing its rate. It is also true that, if the venous inflow is inadequate, i.e., the heart chambers are not completely filled at the end of diastole, or are just filled and no more, simply increasing the frequency of beat, as by raising the temperature, fails to increase the output. This is obvious, since if the beats have been occurring at the end of a period of rapid filling and no increase in venous inflow occurs as the rate increases, the acceleration in heart rate must be accompanied by a proportional reduction in the volume of blood ejected per beat. The reduction in stroke volume with rise in rate is shown in table

more completely. In moderate exercise, in man, for example, the diastolic size of the heart as observed radioscopically may not increase, whereas the systolic size is less than that during rest.

The experiments of Starling and his colleagues have shown that the dog's heart is capable of pumping in the neighborhood of 57 times its own weight of blood per minute for a considerable length of time. In one instance a heart weighing 42 grams gave an output of 2400 cc. per minute. If the power of the human heart may be taken to be equally great in proportion to its weight, then a heart weighing 300 grams or so should be capable of an output of over 17 liters per minute. The maximal output actually observed in man by indirect methods is more than double this figure (p. 225).

TABLE 18

Dog. 8.5 kilos. Weight of heart 77.5 gm. Small constant venous inflow, heart rate increased. The output remains unchanged
(Markwalder and Starling)

TIME	TEMPER- ATURE	RATE OF HEART PER MINUTE	ARTERIAL PRESSURE	SYSTEMIC OUTPUT	CORONARY SINUS OUTPUT	TOTAL CORONARY OUTPUT (CALCULATED)	TOTAL OUTPUT (CALCULATED)	OUTPUT PER HEART BEAT	VENOUS PRESSURE
	°C		mm. Hg	cc. per minute	cc. per minute	cc.	cc.	cc.	cm. H ₂ O
2:20	28.2	72	119	612	24.20	40.3	652.3	9.05	11.0
2:28	30.2	90	119	612	20.62	34.4	646.4	7.20	9.0
2:37	33.4	114	119	612	18.46	30.8	642.8	5.63	6.2
2:42	35.0	126	119	625	19.74	32.9	657.9	5.2	5.0
2:50	37.0	144	117	612	21.20	35.3	647.3	4.47	4.2
2:58	39.0	156	116	612	22.90	38.1	650.1	4.16	3.8

18. If, on the other hand, the venous inflow is large, the heart fills earlier in diastole and a period of diastasis (p. 173) is created. Then any increase in rate by abolishing or reducing this period must increase the output (see also p. 224).

Referring again to table 16 in which it is seen that the increased output is unaccompanied by a notable acceleration of the heart, it must be remembered that the experiments were carried out upon a denervated heart-lung preparation; the Bainbridge reflex (p. 210) was in consequence abolished. It cannot be concluded therefore that in the intact animal the rise in venous pressure which resulted from the greater inflow would not have caused an increase in the rate of the heart. In the intact animal a moderate increase in the output may also be brought about without an increase in the diastolic volume, the ventricles simply emptying

THE SOURCE OF THE ENERGY WHICH ENABLES THE HEART TO INCREASE ITS OUTPUT. THE LAW OF THE HEART

It is well known that skeletal muscle contracts more forcibly if it is loaded by a weight before it is excited. The weight stretches the muscle fibers, i.e., it increases their length and exerts a certain tension upon them. If the muscle is made to contract isometrically the tension developed during the contraction is found to be proportional to the length of the muscle before excitation. The latter is called the *initial length* of the muscle. The tension which the load exerts upon the fibers just prior to their contraction is spoken of as the *initial tension*. The tension developed when the muscle contracts—isometrically—will be referred to as the *developed tension* which, of course, is a measure of

the force of the contraction. When a resting muscle is weighted, little change in initial tension actually occurs until it is extended beyond a length corresponding to that which it possesses when in its natural position in the body, i.e., at its physiological length. Up to this point the developed tension increases with each increment in initial length, but beyond it the developed tension actually becomes less with increasing initial length. Yet, it is only when the muscle is stretched beyond its physiological length that any marked increase in initial tension occurs. The power of contraction of a skeletal muscle is therefore dependent upon initial length and not upon any stimulating effect exerted upon the muscle fibers by initial tension. The relationships between the initial length, initial tension and the developed tension of skeletal muscle during its contraction are shown in figure 98a.

There has been some controversy as to whether the energy liberated by the cardiac muscle is, like skeletal muscle, dependent mainly upon initial length or upon initial tension. The experiments of Starling and his colleagues indicate that initial length is the sole determining factor.

Clearly, there are no means, as in the case of skeletal muscle, by which the length and tension of the cardiac muscle during its relaxation (diastole) or the tension developed during contraction (systole) can be measured *directly*. Yet, the diastolic volume depends upon fiber length (initial length): the intraventricular pressure during diastole represents initial tension, and the pressure developed during systole is related to the tension set up by the contracting fibers (developed tension). When, therefore, simultaneous records of diastolic volume and intraventricular pressures (p. 173) during diastole and systole are secured, the data may be plotted as shown in the diagram (fig. 98b) with volume (cc.) representing initial length, along the ordinates and pressure (mm. Hg) representing tension, along the abscissae. The venous pressure which stretches the cardiac muscle during diastole corresponds to the weight applied to the skeletal muscle. The opening of the semilunar valves against the aortic pressure represents the load against which the cardiac muscle has to contract. It will be seen from the figure that the force of the ventricular contraction increases with the diastolic volume until the heart becomes overdistended and a rise in diastolic pressure occurs. The force of the contraction then falls off (compare with fig. 98a), the two curves approaching one another and finally meeting.

Starling has expressed this fundamental principle of cardiac behavior in what has been termed the *Law of the Heart*, namely, that "the energy set free at each contraction of the heart is a simple function of the length of the fibers composing its muscular walls." Thus the heart fibers automatically gain the necessary energy to eject the greater load of blood which fills its cavities during diastole or to discharge its contents against a raised arterial pressure. In the latter instance the ven-

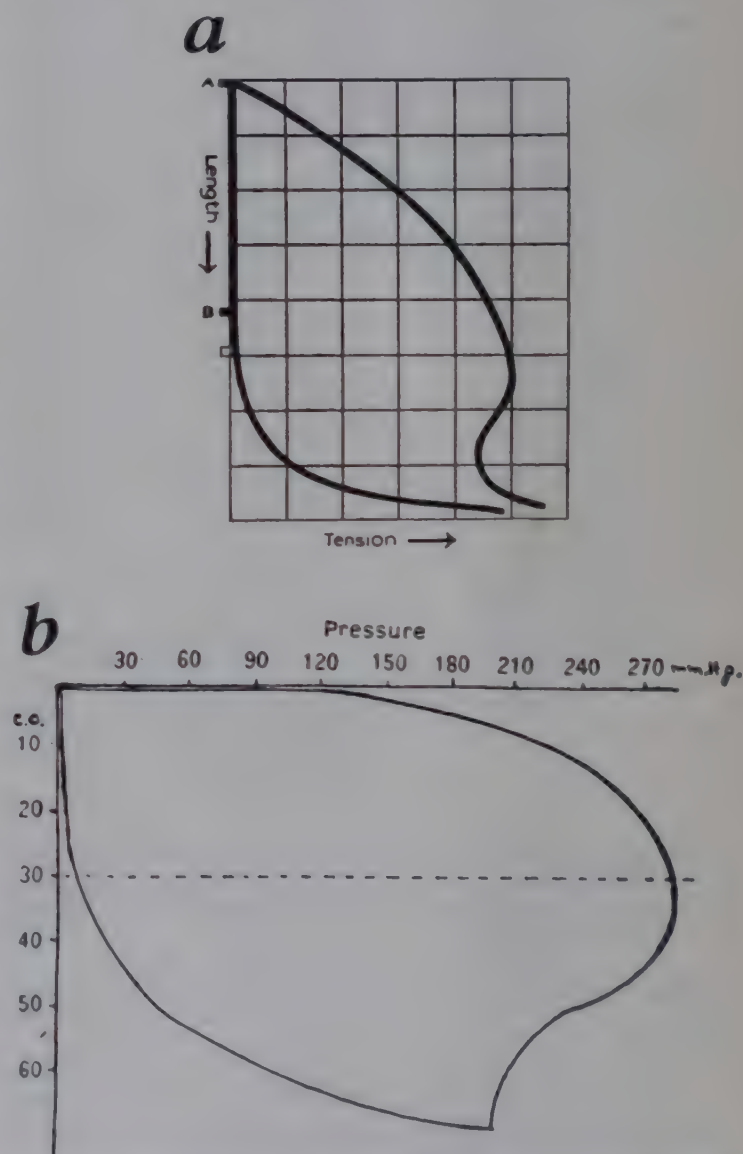


FIG. 98. Showing (a) the relation of initial length to the tension developed by skeletal muscle contracting isometrically, and (b) the relation of diastolic ventricular volume (initial length) to systolic pressure (see text). (After Starling and associates.)

tricle for the first beat or two after the pressure has been raised does not expel the full quantity of blood, but retains a part; this serves to increase the diastolic volume beyond that existing before the pressure was raised, and so to increase the force of the subsequent contraction. The greater energy liberation associated with the increased diastolic volume is attributed to the greater extent of chemically active surface which naturally results from elongation of the fibers.

The results of the experiments of Anrep and Segall are also confirmatory of Starling's conclusions. These observers found that when the isolated frog's ventricle contracted isometrically the contractile force, up to a point (systolic pressure), increased proportionately with the filling of the ventricle (diastolic volume); the maximal tension developed when the ventricle was filled to $\frac{2}{3}$ of its maximal capacity. Filling beyond this caused a rise in the initial (diastolic) tension accompanied by a reduction in the developed tension (fig. 99). Katz was able to dissociate the effects of these two factors upon the development of tension by the turtle heart. When initial tension was varied but initial length kept constant, or the converse, or when both were varied in the same or in opposite directions, the results always indicated that initial length was the factor which determined the force of the contraction. Changes in initial tension amounting to over 200 mm. H₂O were usually without effect upon the height of the intraventricular

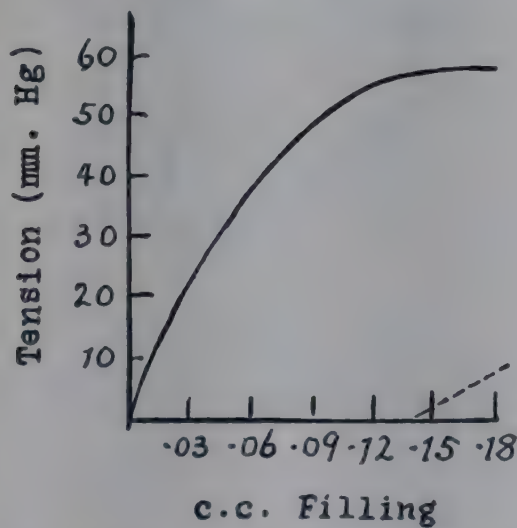


FIG. 99. Showing the effect of graded increases in filling of the frog's ventricle upon the tension developed in isometric response; --- initial tension. (Redrawn from Anrep and Segall.)

pressure provided the diastolic volume was kept constant.

It has also been shown by Starling and Visscher that the oxygen consumption of the heart muscle, i.e., the total energy expenditure, is directly proportional to fiber length (diastolic volume). The ratio $\frac{\text{O}_2 \text{ consumption}}{\text{diastolic volume}}$ remained constant though diastolic volume varied widely. The work performed by a heart in first-class physiological condition also bears a linear relationship to diastolic volume and consequently to the oxygen consumption. On the other hand, when as a result of fatigue the condition of the heart deteriorated, its diastolic volume was much greater in proportion to the work performed than was the case with the well-conditioned heart, i.e., the ill-nourished muscle fiber in order to gain energy for the performance of a given amount of work must

be stretched to a greater extent. Nevertheless, whether the condition of the heart muscle was good or bad the relationship between oxygen consumption and diastolic volume was the same (fig. 100). This means, clearly, that for the performance of a given piece of work the poorly nourished heart uses more oxygen (since it dilates more) than does a heart in good condition; or put

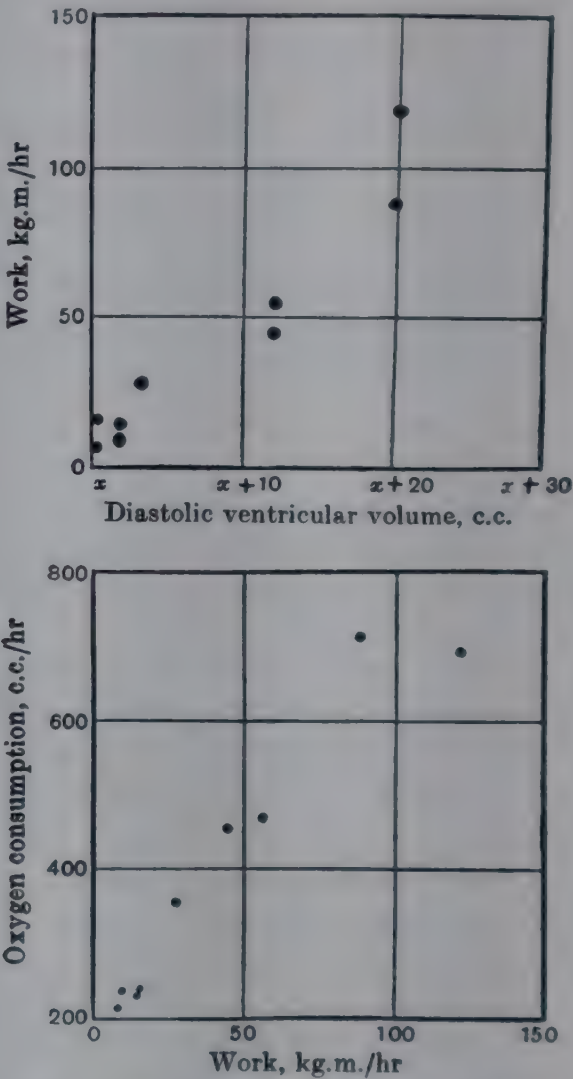


FIG. 100. Lower chart shows the work done plotted against the oxygen consumed. In calculating the work of the heart the velocity factor (p. 116) was neglected. Upper chart gives data from the same experiment, work being plotted against the diastolic volume of the ventricles. The volumes are expressed as x plus known values. The x represents the lowest value of the volume during the experiment, which is impossible to measure when a cardiometer is used to record heart volume. The cardiometer enables one to measure only an increase over this minimum value. The figure shows a direct correspondence between work done and ventricular volume. (After Starling and Visscher.)

in another way, the proportion of the total energy expenditure which appears as mechanical work (efficiency) is lowered when the heart muscle departs from its prime physiological state.

PATHOLOGICAL PHYSIOLOGY OF CARDIAC LESIONS.
CARDIAC DILATATION AND HYPERTROPHY

The enlargement (dilatation and hypertrophy) of the diseased heart is a compensatory reaction.

In aortic regurgitation, for example, the heart receives blood not only from the auricles but also from the aorta as a result of the incompetence of the aortic valves. The diastolic enlargement of the ventricular cavity which is required for the accommodation of the greater blood mass also enables the heart to develop the energy necessary for the ejection of the extra blood during systole.

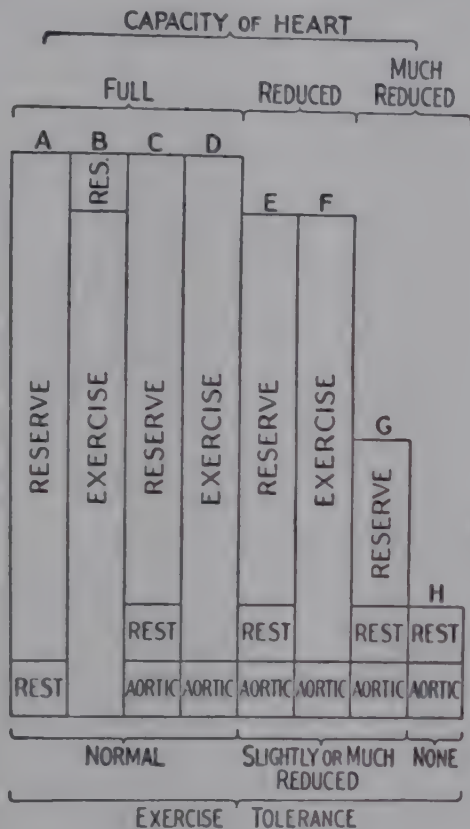


FIG. 101. Diagram illustrating the reserve of the normal heart and of the heart in aortic regurgitation (after Lewis). In column A the reserve power of the normal heart, i.e., its capacity for work is represented as being several times greater than that required for rest. In column B the greater proportion of, but not all, the reserve is drawn upon to perform the extra work entailed in strenuous muscular exercise. Column C represents the heart in aortic regurgitation but with an efficient myocardium. It will be noted that the work required of the heart during rest is increased but its reserve is diminished to only a small extent; it is therefore capable of performing the extra work required for vigorous muscular exercise (column D). In columns E and F the reserve of the heart muscle is represented as falling short of the requirements of strenuous exertion. The reserve is reduced still further in column G, and in column H it has gone entirely, the heart muscle being capable only of meeting the requirements of rest. The subject is dyspneic during rest, and congestive heart failure is imminent or has already supervened.

Cardiac dilatation therefore whether under physiological conditions (physiological dilatation) or in association with heart disease (pathological dilatation) is the means whereby the heart mobilizes its reserves of energy (fig. 101). The so-called reserve power of the human heart, i.e., its capacity for work, resides in the extensibility of its muscle fibers, within the physiological limit. It is apparent then that the nearer the fiber during diastole

approaches its maximal physiological length the greater will be the encroachment upon the heart's reserve. A well-developed and efficient heart in order to gain sufficient power to accomplish a certain amount of extra work need dilate relatively little and is capable of discharging easily as much blood as it receives. The venous pressure in consequence shows little tendency to rise and the pulse is not greatly accelerated. On the other hand, the smaller heart or the heart with a myocardium weakened by disease, ill-nourishment or oxygen lack, when given an equivalent amount of work to perform must dilate to a greater extent in order to liberate the required energy. Indeed, an ill-equipped heart may, as a result of some extra burden, be dilated to its physiological limit and still be unable to increase its output per beat. The heart accelerates its beat as this point is approached (Bainbridge reflex) in order to increase its output. When the full physiological length of the fiber has been attained and the optimal pulse frequency developed, the heart has reached the limits of its powers. Blood then accumulates in the cardiac chambers, the venous pressure rises, the circulation through the capillaries is slowed and the blood gives up a greater proportion of its oxygen load to the tissues (stagnant type of anoxia, pp. 147, 221 and 359).

THE PERMANENT EFFECTS OF EXERCISE UPON THE HEART

The belief has been widely held that strenuous muscular effort is conducive to cardiac dilatation and hypertrophy. A proportion of athletes have, of course, suffered from heart disease and an occasional racehorse has died with a dilated and hypertrophied heart. Instances of this sort have been cited in support of such a view. It is now agreed, however, that the cardiac enlargements under these circumstances are the result of preexisting disease and that the healthy heart cannot be dilated beyond its physiological limit, nor will a bout of strenuous exercise "strain" the healthy heart muscle or cause it to fail. In a healthy person the functional capacity of the heart and of the skeletal musculature are apparently so proportioned to one another that the greatest venous inflow which the muscles can provide is taken care of by the reserves of cardiac energy. The healthy heart of the marathon runner or oarsman does not hypertrophy to a pathological degree. It has also been shown by X-ray examination that the diastolic diameters of the healthy heart are not materially increased during strenuous exercise and that the

systolic size is actually less than it is during rest; that is, the heart empties more completely. It may, therefore, be concluded that acute dilatation or chronic dilatation with hypertrophy is the result of some diseased state of the heart itself.

It should not be concluded, however, that muscular training exerts no effect upon the size of the heart. Mitchell, for example, found that the heart-size of a group of undergraduates at Cambridge underwent a gradual increase over a period of a few years of athletic training. This was accompanied by a reduction in pulse rate (see p. 224). Lindhard observed an increase of 20 per cent in the resting cardiac output as a result of physical training. Others have reported more marked effects in persons indulging in very arduous types of athletics. Eyster, on the other hand, could demonstrate no increase in the average heart size of a group of young athletes when compared with that of a group following a more sedentary life. The evidence taken in review indicates that athletic pursuits, especially of a strenuous nature, may cause a moderate but definite increase in cardiac bulk. This, however, is purely physiological and is proportioned to, or only slightly in excess of, a development of the skeletal muscles. That is, to say, the normal ratio of heart weight to body weight shows no change or a very moderate one.

THE NATURE AND CAUSE OF THE HYPERTROPHY IN CARDIAC DISEASE

The average weight of the normal adult heart is 300 grams (250 to 350); it constitutes from 0.40 to 0.50 per cent of the body weight. In disease 500 grams is not an unusual weight and hearts weighing 1000 grams or more are occasionally seen. The commonest causes of cardiac hypertrophy are valvular disease and hypertension. In the latter, the left ventricle is primarily involved but in valvular disease one or other ventricle, or both ventricles may be enlarged; in some instances the auricles are also dilated and their walls hypertrophied. Other less common causes of cardiac enlargement are coronary disease, arterio-venous aneurysm, hyperthyroidism, adherent pericardium, anemia and congenital cardiac defects. When the enlargement is due predominantly to hypertrophy it is sometimes referred to as *concentric*, when marked dilatation exists as well, the enlargement is said to be *eccentric*. The increased bulk of the ventricular muscle is due, not to a multiplication of its fibers, but to an increase in the size of each fiber. The sarcoplasm is more abun-

dant and the fibrillae more numerous. There is also frequently an increase in the connective tissue between the fibers.

The hypertrophy is probably always preceded by some degree of dilatation. The permanent lengthening of the fibers consequent upon the latter, as already mentioned, tends to reduce the cardiac reserve since they are thereby brought nearer to the point of maximal extension. The hypertrophy, on the other hand, has the effect of increasing the power of the fiber at this new length with the result that the heart's reserve power is raised and may be restored nearly to its normal value (fig. 101). Such a heart is said to be compensated. In experimental lesions the hypertrophied heart is reported to have a reserve power quite as great as that of the normal heart.

The *cause of the cardiac hypertrophy* is not easily explained. Increased work (induced by valvular defect, hypertension, etc.) is not the only, or even perhaps the major, factor in its production. In the first place, the extra burden thrown upon the heart by a valvular lesion is often not sufficient to encroach to any great extent upon the reserve power of the heart and the grade of hypertrophy is very often out of proportion to the amount of extra work which the heart is called upon to perform. Arterial hypertension if it develops gradually may, for example, cause little hypertrophy though the work of the heart is increased by 40 per cent. Also, in a large proportion of cases of mitral stenosis the hypertrophy of the left ventricle is as great as that of the right where the burden falls, and in aortic disease the right as well as the left ventricle may be increased in bulk (Lewis). Finally, cardiac hypertrophy occurs, as in coronary disease, when there is no evidence of increased work.

The experiments of Eyster and his associates throw some light upon this question. They produced aortic regurgitation in dogs by passing an instrument down the right carotid artery to the heart and cutting the aortic valves. The ventricle, being suddenly subjected during its relaxation phase to the high aortic pressure, became acutely dilated. The dilatation (as shown by roentgenograms) disappeared within a few days but hypertrophy gradually developed from then on. An effect comparable to aortic stenosis was also induced by constricting the ascending aorta with a rubber band. Similar changes in heart size resulted. In other animals the band was removed after from 3 to 6 days, at which time the ventricular dilatation had reached its maximum.

Though the heart was relieved of the extra work, hypertrophy was not prevented. This came on gradually, as in those instances in which the stenosis was not relieved, and was complete by about the eightieth day. A second constriction again caused immediate dilatation followed by progressive hypertrophy. Similar results were obtained by massive transfusions which caused distension of the right ventricle. Histological examination of the heart during the stage of dilatation revealed thinning and hydropic degeneration of the heart muscle, which were ascribed to the injurious effect of the acute stretching of the muscle fibers. In the later stages the degenerative changes had disappeared and a pure hypertrophy alone was evident. The hypertrophy was therefore considered to be a reaction to injury brought about by the sudden dilatation.

These observations are of the utmost importance in gaining an insight into the probable sequence of events in the hypertrophy of the human heart. Overstretching of the fibers is apparently associated in some way with their overgrowth. The increased fiber length may be brought about by an excessive load resulting from some mechanical defect such as aortic regurgitation. Injury to the muscle is thereby induced. Or, on the other hand, the overstretching may be the result of a primary weakening of the myocardium, as in coronary disease or infective or toxic processes, the fiber being forced to lengthen unduly in order to liberate the required energy. The manner in which increase in fiber length brings about the overgrowth is unknown, but the experiments of Starling and Visscher suggest elevation of the metabolism of the muscle as a possible explanation (p. 218). It has been mentioned that, for the performance of a given amount of work, the ill-conditioned myocardium as compared with a healthy one has a much greater oxygen consumption. This view accords with the facts that a diseased myocardium may hypertrophy even though its work is not at all increased, and that a great increase in the burden of the healthy muscle can be borne with only a very moderate degree of overgrowth.

HEART FAILURE ("CARDIAC DE-COMPENSATION")

When the heart is unable to maintain an efficient circulation during rest or mild exertion the condition is spoken of as heart failure. In most instances signs of venous congestion—increased venous pressure, capillary engorgement, edema,

etc.—appear, the term *congestive heart failure* being then applied.

The heart with a valvular defect or one which is forced to work against some abnormal resistance may, if it possesses healthy muscle, continue to perform its functions efficiently for years. The state of the heart muscle rather than the valvular lesion itself has come to be recognized as the important factor determining the onset of cardiac failure. The healthy myocardium possesses such great reserves of energy that there is little likelihood of its ever being faced with a resistance which it cannot effectively overcome—not until the myocardium itself becomes diseased do the signs of circulatory failure make their appearance.

Increased resistance to the output of the right ventricle results from such pulmonary conditions as emphysema or fibrosis of the lung; from pulmonary or mitral stenosis; or from failure of the left ventricle. Aortic stenosis, hypertension, or congenital narrowing (coarctation) of the aorta increases the resistance to the output of the left ventricle.

CAUSES OF CARDIAC FAILURE

Circulatory failure may be precipitated by the reduction in the myocardial reserve of a heart which has been working against some inordinate resistance or at a mechanical disadvantage; or it may be the result of an increase in the burden of a heart whose reserve has already been lowered by myocardial disease. Among the commoner causes are:—

(a) Infections, especially of the respiratory tract. The increased cardiac work resulting from the rise in metabolic rate caused by the fever, direct poisoning of the myocardium, and cough all conspire to reduce the cardiac reserve to the point where the failure ensues.

(b) Excessive muscular effort.

(c) Chronic pulmonary conditions, emphysema, bronchitis, etc., accompanied by much coughing which exerts its effect mainly through the muscular effort involved.

(d) Pregnancy.

(e) Rapid heart action, e.g., auricular fibrillation, paroxysmal tachycardia, etc. It should be remembered that the heart works very uneconomically at high rates of beating, i.e. the heart expends more energy for the performance of a given amount of work at high than at low rates of beating. One reason for this is that the cardiac cycle is shortened mainly at the expense of the diastolic (rest) period and the period of ejection (time during which work is actually performed). The period of isometric contraction (during which energy is ex-

pended in raising the intraventricular pressures above the arterial pressures but no work is done) is shortened comparatively little. This latter period is, therefore, in a sense a waste period, and its total time per minute is greater the more rapid the heart rate.

(f) Hyperthyroidism.

On the other hand, the heart muscle may be so weakened by disease—coronary sclerosis, acute infective processes, severe anemia, anoxia—that cardiac failure ensues though no valvular defect or other condition exists to increase the work of the heart.

The validity of the application to clinical cases of Starling's law of the heart, which was based upon acute animal experiments, has been tested by Starr and his associates. The work of the heart, as determined in 140 normal persons and in a number of patients who had recovered from congestive heart failure, was plotted against the heart volume. The work of the heart was calculated from the cardiac output and the blood pressure; the heart size was determined roentgenologically. In the cardiac patients, the work performed for a given heart volume was much less than in normal subjects. These authors concluded that Starling's law holds true for the human heart in congestive failure.

There is some difference of opinion concerning the fundamental cause of cardiac heart failure. According to one view (Katz and his associates) the total energy liberation of the heart muscle (see p. 192) at a given fiber length is reduced to the point where an adequate circulation cannot be maintained. Visscher, on the other hand, considers that, in the majority of cases at any rate, the heart fails because of a decrease in its mechanical efficiency (that is, because of a reduction in the proportion of the total energy output which is expended in doing useful work). Starling and Visscher found that this was invariably the cause of cardiac failure in the heart-lung preparation of the dog. In one of their experiments of 4-hours duration, the oxygen consumption rose from 360 cc. to 590 cc. per hour, the diastolic volume increased by 42 cc. and the efficiency fell from 9.5 per cent to 5.8 per cent.

THE SIGNS AND SYMPTOMS OF CONGESTIVE HEART FAILURE

The chief manifestations are: increased venous pressure; dyspnea; cyanosis; congestion and consequent enlargement of the liver and spleen, pulsation of the liver is not uncommon, and there

may be jaundice; oliguria and albuminuria; and edema.

The manner in which the chief signs and symptoms of cardiac failure are produced has been a question of some controversy. According to one view—the *forward-failure theory*—they are the result of a reduced cardiac output and consequent diminished flow of blood through the tissues. The dyspnea, for example, has been attributed to slowing of the circulation through the medulla (respiratory center); the cyanosis to the diminished flow through the vessels of the skin and the greater coefficient of oxygen utilization; the edema to increased capillary permeability induced by the local asphyxia. In cardiac failure resulting from paroxysmal tachycardia, heart block, or acute myocardial disease, there may be a marked reduction in the cardiac output and in these instances the manifestations may be explained upon the forward-failure theory. In the majority of cases of heart failure, however, the clinical picture is interpreted best upon the basis of the *backward-failure theory* ("back-pressure" theory), which may now be briefly stated. As the myocardium fails, blood accumulates in the ventricle which in consequence dilates. The muscle fibers become stretched to a point where they offer a greater resistance to the incoming venous blood, a rise in auricular pressure follows which is transmitted backwards. The heart does not fail as a whole; failure of the left ventricle may precede failure of the right by a considerable interval or death may occur from failure of the left or the right ventricle alone.

When the left ventricle fails first and does not adequately discharge its contents the pressure of blood in the left auricle and pulmonary veins rises. The high pressure in the pulmonary circuit causes engorgement of the vessels of the lung. The total volume of blood in the lungs is greatly increased and the velocity of flow in the individual vessels diminished. The distended vessels encroach upon the air spaces, the vital capacity is reduced, the lung tissue is rendered less expansile, dyspnea and cough result (p. 355). Increased resistance in the pulmonary circuit, such as results from stenosis of the mitral orifice, even in the absence of left ventricular failure tends also to cause pulmonary engorgement accompanied by dyspnea and cough, especially upon exertion. Pulsus alternans (p. 202), gallop rhythm (p. 179) and cardiac asthma are characteristic features of left ventricular failure.

So long as the right ventricle continues to con-

tract forcibly and discharge its contents against the increased resistance in the pulmonary circuit, the systemic vessels are not congested. Subsequent failure and dilatation of the right ventricle are attended by a rise of right auricular pressure and of the pressure in the systemic veins, with congestion of the liver and abdominal viscera. Signs and symptoms (edema, cyanosis, etc.) appear, due to engorgement of the peripheral vessels and slowing of the blood flow through them. But, though the velocity of the blood in the peripheral capillaries is reduced, owing to their distension and the consequent general enlargement of the capillary bed the total volume of blood flowing through the periphery may show little change (see p. 148).

The following observations militate against the forward-failure hypothesis as an explanation of the manifestations of the usual type of cardiac failure, and argue for the "back-pressure" conception.

(1) Reduction in the circulation rate, though commonly, is not invariably associated with congestive heart failure; the reduction in cardiac output, when a reduction does occur, does not run parallel with the severity of the symptoms. Moreover, the improvement of the clinical condition which follows the administration of digitalis is not always attended by an increased circulation rate.

(2) The fact that one ventricle can fail independently of the other and that left-sided failure is associated with pulmonary congestion and right-sided failure with systemic congestion can be explained upon the basis of "back-pressure," but not by the forward-failure hypothesis (reduced cardiac output). The reduction in vital capacity in failure of the left ventricle or in obstruction (stenosis) at the mitral orifice is accounted for most satisfactorily by a rise of pressure in the pulmonary circuit and congestion of the lungs. Congestion of the lungs and diminished expansibility, as a result of compression of the pulmonary veins, have been demonstrated in animals.

(3) Venesection, a valuable therapeutic measure in congestive heart failure causes a reduction of the cardiac output.

(4) Reduction of the cardiac output in animals does not reproduce the ordinary picture of heart failure.

(5) Edema cannot be satisfactorily explained by the forward-failure hypothesis. The edema fluid is of very low protein content which is in accord with the view that it is formed as a result of increased filtration pressure.

If it were the result mainly of capillary damage the protein content would be nearer that of plasma.

The backward-failure theory does not necessarily imply that the auriculo-ventricular valves become incompetent (tricuspid in the case of right-sided failure and mitral in the case of left-sided failure) with consequent regurgitation of blood into the right or left auricle. Auricular pressures can be raised without the occurrence of any actual backward leakage of blood.

The inefficiency of the heart in congestive failure. For the performance of a given amount of work the oxygen usage of the subject of congestive heart failure is considerably higher than that of a healthy person. From experiments upon animals (p. 218) one would suspect that the heart is responsible to some extent at least for the higher oxygen consumption. Resnik and Friedeman found that the basal metabolism of patients with heart failure was from 10 to 60 per cent above normal, and that improvement in the cardiac condition was accompanied by a reduction in the amount of oxygen consumed. They conclude that increased respiratory effort (i.e., the increased work of the respiratory muscles) accounts for the greater part, but that a considerable share of the extra oxygen is used by the heart itself. Other factors which have been suggested as being responsible, e.g., thyroid stimulation as a result of circulatory alterations in the gland, apprehension and discomfort, or expansion of the capillary bed caused by the high venous pressure, played no rôle in the opinion of these authors in producing the high metabolic rate.

Exercise tolerance tests. A useful test of cardiac function in heart disease based upon the metabolic response to exercise has been devised by Katz and his associates. The greater proportion of the increased oxygen consumption occurs after the exercise. These observers, therefore, determine the oxygen consumption before, during and for 15 minutes after the performance of a measured amount of work. The total oxygen consumption throughout the test is compared with that for the same period at the pre-exercise rate. The difference between the two estimations gives the excess metabolism (p. 620) of the exercise which is expressed in cubic centimeters of oxygen consumed per kilogram-meter of work per square meter of body surface. A simple but valuable aid in estimating cardiac reserve is the determination of respiratory and cardiac acceleration after a standard light exercise, e.g., 50 hops 3 inches from the floor at one second intervals.

CHAPTER XXVI

THE OUTPUT OF THE HEART

DEFINITIONS AND GENERAL CONSIDERATIONS

The output of the heart per beat is spoken of as the *systolic discharge* or the *stroke volume*, and the output per minute as the *minute volume* or the *circulation rate*. The value of the latter is simply the product of the stroke volume and the pulse rate (pulse rate \times stroke volume = minute volume) and the minute volume divided by the pulse rate gives the stroke volume. The quantity of blood ejected by each beat of the left ventricle in the average healthy man during rest is from 60 to 70 cc. An equal quantity is, of course, discharged at the same time by the right ventricle, making a total for the whole heart of from 120 to 140 cc. The contents of the left ventricle are ejected against a much higher mean arterial pressure than the contents of the right; the mean pressure in the pulmonary artery being about $\frac{1}{3}$ of that in the aorta. The minute volume is usually expressed in terms of one ventricle. The output of one ventricle obviously represents the quantity of blood flowing through the lungs, or through the systemic vessels, during the same period. It is for this reason the value expressing the minute volume of the ventricle is referred to as the circulation rate.

It is evident that the heart can increase its output per minute by increasing its stroke volume and maintaining its rate constant or, conversely, by increasing its rate and maintaining a constant stroke volume. Again, both these factors may be called into play. When the heart rate accelerates the output per beat can be kept constant only if the venous inflow is adequate and so, only under such circumstances can the minute volume be increased. If, for example, the beats of the heart have occurred at the end of a period of rapid filling, i.e., before or at the moment that the heart chambers are filled, simply increasing the heart rate will cause the beats to fall earlier in the period of rapid filling. Reduction in the stroke volume in proportion to the increase in rate must result and no increase in the minute volume can, therefore, occur (see table 18, p. 216). At very rapid heart rates, as in paroxysmal tachycardia, a point is reached at which the heart does not relax sufficiently between beats to take on an adequate load of blood and the minute volume becomes reduced.

If, on the other hand, the beats have been occurring some time after the period of rapid filling, i.e., a period of diastasis exists, then an increase in heart rate will, by shortening or abolishing this period, or by preventing its appearance when the inflow is augmented, increase the output. Consequently, when the venous return is increased as in muscular exercise, the greater mass of blood is readily accommodated by the large well-developed heart and there may be no period of diastasis, no rise in venous pressure; the heart rate then shows less tendency to increase. The hearts of some athletes show no increase in rate, whatever, during exercise; the resting stroke volume of such hearts may be double or more that of an ordinary person, namely 120 to 130 cc. In the smaller heart the greater inflow causes the heart to fill earlier in diastole, the venous pressure rises and as a result of the Bainbridge reflex the heart accelerates. Little change in stroke volume may occur, the greater minute volume being brought about almost entirely by an increase in the frequency of the beats. In the majority of healthy persons both factors—increase in heart rate and increase in stroke volume—play a part in the production of a greater cardiac output. Individuals differ, however, in the extent to which each factor contributes. In the athlete, as just mentioned, the output is increased chiefly through an increase in the stroke volume; increase in heart rate plays a very minor rôle, whereas in the sedentary individual the latter factor exerts an important effect.

The contribution which cardiac acceleration can make toward the minute volume is strictly limited, for from 180 to 200 is about the maximum rate to which the healthy heart can be speeded up. This is only about $2\frac{1}{2}$ to 3 times the normal rate. With a constant stroke volume, therefore, cardiac acceleration could not increase the minute volume more than two and a half to three times. In muscular exercise, the oxygen consumption is increased many fold. There are only two possible means whereby the tissues can be supplied with the extra oxygen, namely, by an increased circulation rate or a greater coefficient of oxygen utilization (i.e., the removal of more oxygen from each unit of blood, p. 322). Were the cardiac output

solely dependent upon a rise in pulse rate, then the circulatory factor could, obviously, increase the supply of oxygen to the tissues three times, at the most, over that of the resting state. If no change in the stroke volume occurred, then, in order to increase the oxygen supply, say 10 times, the coefficient of oxygen utilization would require to be increased between three and fourfold. As a matter of fact, the cardiac output in a robust subject may increase 9 times during strenuous exercise, and the oxygen consumption 12 times. In such an instance it must be concluded (1) that the stroke volume increases over 3 times (even at a maximum pulse rate), and (2) that the oxygen requirement is satisfied largely by a rise in the circulation rate, an increase in the coefficient of oxygen utilization playing a less prominent rôle.

The proportion in which each of the two factors just mentioned—increased circulation rate and increased coefficient of oxygen utilization—contribute in bringing about the greater oxygen supply to the tissues varies, however, in different persons and with the type of exercise. In very light exercise involving slow movements the coefficient of oxygen utilization is increased to a proportionately greater extent than is the cardiac output. With moderately severe exercise, on the other hand, the coefficient of oxygen utilization is usually about doubled while the cardiac output is increased fourfold or so. This would permit an eightfold increase in oxygen consumption. As the exercise becomes more severe the circulation rate increases to a less extent proportionately than the coefficient of oxygen utilization, and in exhausting effort a point is reached where the cardiac output shows no further increase, the coefficient of oxygen utilization from then on rising with the oxygen consumption. The rise in the coefficient of oxygen usage in muscular exercise is attributed to the diversion of a larger proportion of the total blood volume through the contracting muscles. The production of acid metabolites (carbon dioxide and lactic acid) and the rise in temperature also lower the affinity of the hemoglobin for oxygen which, in consequence, is given up more readily (p. 321) to the tissues.

The extent to which these two factors operate to satisfy the oxygen requirement also varies with the particular muscle groups which are exercised. Muscles, such as those employed in walking or running, whose action is more efficient in increasing the venous return tend to increase the cardiac output more than those which have

not this effect, even though the total oxygen consumption in both instances is the same. Swimming is an exercise which causes a relatively great increase in the cardiac output. Several factors other than the exercise itself, namely, increased heat loss, respiratory stimulation and the pressure of the water are largely responsible for the greater cardiac response in this type of exercise. There is some evidence that, as a result of training, the coefficient of oxygen utilization tends to increase during exercise, thus sparing the work of the heart.

THE OUTPUT OF THE HEALTHY HEART. NORMAL STANDARDS. PHYSIOLOGICAL VARIATIONS

The minute volume of the heart under basal conditions¹ varies, in different individuals, from 3 to 4.6 liters. The value for a given person was found by Grollman to be remarkably constant, determinations made from time to time varying by no more than 2.5 per cent. Grollman has also shown that the basal cardiac output is a function of the surface area of the body. For normal persons the minute volume per square meter of body surface—the *cardiac index* as it is termed—has an average value of 2.2 liters. In a group of 50 normal adults the index had an average deviation from the mean of 6.4 per cent. The cardiac output then is proportional to the basal metabolism (p. 533) and like the latter can be predicted for a normal person, with a small error, from the surface area. The average basal cardiac output per kilogram of body weight is 62 cc. As already mentioned the average volume of blood ejected per beat (stroke volume) is from 60 to 70 cc.

The following physiological conditions vary the cardiac output.

Muscular exercise. In strenuous exercise the output increases from the basal level of between 3 and 4.6 liters per minute to from 19 to 37 liters, according to the individual; the stroke volume increases from a resting value of from 60 to 70 cc. to from 100 to 200 cc.¹ The effect of muscular exercise upon the circulation rate is considered in more detail above.

Temperature. No change in cardiac output occurs until the environmental temperature exceeds 30°C. Temperatures above this cause a very moderate increase (5 to 30 per cent) in minute volume.

Digestion of food causes an increase above the

¹I.e., with the body recumbent and at rest, at room temperature 20°C and 12 hours after having partaken of food or drink (p. 533).

basal level of from 30 to 40 per cent. This level is reached about 1 hour after the meal, persists for about 3 hours and then gradually declines. The extra strain placed upon the diseased heart following a meal probably accounts for the attacks of angina pectoris (p. 280) which sometimes occur at this time. Ingestion of fluids also increases the cardiac output to a moderate degree. Both the cutaneous and splanchnic regions share in the increased blood flow.

Variations in oxygen and carbon dioxide tensions in the inspired air (pp. 213 and 214).

Sleep causes no reduction in the minute volume below the basal level.

Posture. Schneider and Crampton find that the minute volume is somewhat greater in the recumbent than in the erect position with the subject standing quietly. After prolonged standing, in most healthy persons the output of the heart remains unchanged or decreases slightly. In certain subjects, who upon prolonged standing show poor circulatory compensation for the effect of gravity (p. 139), the pulse pressure decreases by 20 mm. Hg or so and the cardiac output is reduced markedly; fainting may occur.

Emotional excitement, anger, fear, etc., cause a slight increase which varies in magnitude (from 10 to 25 per cent) in different subjects.

Pregnancy increases the minute volume, but only in the later months; the increase amounts to from 45 to 85 per cent.

PATHOLOGICAL VARIATIONS IN THE CARDIAC OUTPUT

A. Conditions which increase the cardiac output

(1) *Hyperthyroidism.* It has been mentioned that the basal cardiac output is proportional to the basal metabolic rate. It therefore follows that the former will be increased in hyperthyroidism; as a matter of fact the output in this condition is raised from 50 to 100 per cent. The shunting of blood from the arterial to the venous side through the dilated thyroid vessels may possibly be a contributory factor (p. 675) in the production of the increased output. After operation the output falls with the decline in the metabolic rate. Within the last few years thyroidectomy has been employed in angina pectoris and congestive heart failure with the object of lowering the metabolic rate and so of reducing the work of the heart. This mode of treatment is resorted to even though no evidence of hyperthyroidism exists. The thyroid is removed completely; thyroid extract

is then administered with the aim of maintaining the basal metabolic rate at a level a little above that at which signs of hypothyroidism appear (−25 to −30). The operation is of benefit in angina pectoris, but its justifiability in other cardiac conditions is seriously questioned.

(2) *Anemia* (see p. 256) increases the output.

(3) *Anoxemia* increases the cardiac output unless severe or prolonged; then the output declines owing to the injurious effect upon the myocardium.

(4) *Fever.* The increase is due mainly to the elevated metabolism (p. 632).

(5) *Angina pectoris.* During the attacks of pain, the cardiac output is definitely increased over that in the periods between attacks.

(6) *Arterio-venous fistula* (arterio-venous aneurysm). A communication between a large vein e.g., the femoral, and its companion artery results in a fraction ($\frac{1}{3}$ – $\frac{1}{2}$) of the blood ejected from the left ventricle being short-circuited, or shunted, to the right side. The velocity of the blood on the proximal side of the fistula is increased, that on the distal side reduced. Trauma is the most common cause of the condition. A pulsating swelling is frequently present at the site of the anastomosis, the heart rate is elevated, the heart becomes enlarged and, according to Harrison and associates who studied the condition experimentally, the minute volume is increased. An increase of 100 per cent in the cardiac output was found in dogs in which a femoral arterio-venous anastomosis had been produced. Compression of the artery or closure of the stoma causes an immediate reduction in the heart rate. Grollman from studies of the condition in man also concluded that the cardiac output was increased.²

The acceleration of the pulse is ascribed by Lewis and Drury to the reduction in the mean arterial pressure (Marey's law, p. 209) resulting from the leak through the arterio-venous fistula, and not to an increase in venous pressure (Bainbridge reflex). They found that after the administration of atropine, which increased the heart rate to 130 beats per minute, compression of the artery caused a reduction in rate of only two beats per minute. This indicates that the reduced rate, which occurs when the artery is compressed without previous treatment with atropine, is due to a vagal reflex. The enlargement of the heart is

²Ellis and Weiss (Am. Heart J. 1930, 5, 3) observed in patients only a slight tendency towards reduction in the cardiac output when the aneurysm was compressed or after operative cure.

considered to be due to deficient nourishment of the myocardium caused by the lowered aortic pressure and the consequent reduction in coronary blood-flow (p. 220). The effects upon the arterial system of an arterio-venous anastomosis resemble those of aortic regurgitation—low diastolic pressure, high pulse pressure (100 mm.) and collapsing pulse—though the blood in the one case leaks into the ventricle during diastole, in the other into the venous system. Capillary pulsation occurs in both conditions.

B. Conditions which reduce the cardiac output

(1) *Cardiac irregularities.* (a) *Paroxysmal tachycardia.* Barcroft and his associates found the output reduced to half the normal value in a subject of this condition. Before the onset of the attack the pulse rate was 64 per minute, the stroke volume 77.5 and the minute volume about 5 liters. During the attack the pulse rate was 198 and the stroke volume 12.9 cc.; the output per minute was therefore 2.5 liters. (b) In *auricular fibrillation* the output is frequently reduced since this irregularity so often accompanies myocardial failure (see below). (c) In *complete heart block* with an efficient myocardium the output under ordinary circumstances shows little alteration from the normal. Since the pulse rate is from 35 to 40 per minute the stroke volume is elevated well above the normal average (100 cc. or more). In other instances associated with coronary sclerosis and myocardial degeneration, the output is definitely reduced. In other subjects again, though the output during rest is normal, the inability of the heart to accelerate fully prevents an adequate output during muscular exertion.

(2) *Valvular disease and myocardial failure.* In the absence of cardiac failure, a valvular lesion, as a rule, causes little change in the output under basal conditions; a reduction is, however, more likely to be found in mitral stenosis than in other forms of valvular disease. Cases which show no reduction in output under basal conditions may, nevertheless, show a much smaller increase in minute volume in response to exercise than does the normal person, the tissues consequently suffer from oxygen lack and cyanosis may appear. The output also remains above the resting level for some time after the exercise has ceased, whereas normally it falls quickly to its previous value. In other subjects of valvular disease but with an efficient myocardium the cardiac output during exercise is not below normal: but, after the termination of the effort, it, usually, as in the

previous group, returns more slowly than is normal to the resting level. When definite weakening of the myocardium supervenes and other signs of heart failure are present, the basal cardiac output is frequently markedly reduced; in other instances, however little or no reduction in output occurs (see p. 223).

Overweight persons with cardiac failure should be benefited by a reduction in their weight. It has been found by Master and his associates, in a series of persons not suffering from heart disease that a reduction of 16 per cent in oxygen consumption, a 30 per cent, decrease in the cardiac output and an average reduction of 35 per cent in the work of the heart may follow loss of weight.

(3) *Myxedema.* The reduction in the cardiac output is roughly proportional to the depression of the basal metabolic rate.

(4) *Adherent pericardium and pericarditis with effusion.* The reduced minute volume is the result of the mechanical interference with the action of the heart. Adherent pericardium interferes with the normal contraction of the heart. Fluid within the pericardial sac prevents full dilatation of the heart during diastole and thus reduces the volume of blood which it can accommodate.

(5) *Pneumothorax* and other pulmonary conditions in which the intrathoracic negative (suction) pressure is reduced (p. 138).

(6) *Surgical shock.* Reduction in the cardiac output occurs early (p. 258).

(7) *Arterial hypertension.* In some cases the minute volume is reduced, in others, probably the majority, it is within the normal range.

(8) *Postoperative.* A pronounced reduction in the cardiac output occurs for a period of from 1 to 4 days following surgical operation (Snyder).

THE EFFECTS OF CERTAIN DRUGS UPON THE MINUTE VOLUME

Adrenaline and *histamine* increase the oxygen consumption and the cardiac output; the effect upon the minute volume is, however, proportionately greater than that upon the oxygen consumption. *Acetylcholine* whose effects in general are very evanescent causes a slight increase in the minute volume. A decided rise in the cardiac output is produced by *nitrites* which, like *acetylcholine*, cause arteriolar dilatation. The increase in the cardiac output caused by *nitrites* is probably a compensatory effect of the lowered peripheral resistance, whereby the blood pressure is maintained near the normal level. *Digitalis* produces no immediate effect upon the minute volume in normal persons, but a slight increase occurs about 6 hours after administration

of the drug, followed by a reduction which persists for twenty-four hours. In subjects of congestive heart failure with auricular fibrillation the output is as a rule though not invariably increased as the cardiac condition improves. *Strophanthin* acts similarly to digitalis. *Atropine* which increases the heart rate to 150 or 180 beats per minute does not increase, as a rule, the cardiac output. *Alcohol* in moderate dosage (35 cc.) causes no more than a slight rise in the cardiac output. Grollman believes the effect to be largely psychic in origin rather than due to the direct action of the drug upon the heart. *Caffeine* increases the cardiac output; *pituitrin* and *morphine* reduce it slightly.

MEASUREMENT OF THE OUTPUT OF THE HUMAN HEART

Any method for the estimation of the circulation rate in man must, of course, be indirect. Several methods have been devised for the purpose. The methods fall into two groups, (1) those based solely upon the Fick principle, and (2) those which involve as well, breathing a foreign gas, e.g., nitrous oxide, ethyl iodide or acetylene.

THE FICK PRINCIPLE

The output is calculated from the difference between the oxygen (or CO₂) content of the venous blood and that of the arterial blood, and the total oxygen consumption (or CO₂ elimination). It must be evident that if the quantity of oxygen which a unit of blood delivers to the tissues (or takes up from the lungs) be known, together with the total quantity of oxygen consumed over a given period, then the volume of blood which had been engaged in the carriage of this quantity of gas can be calculated. To take an example. The arterial blood contains about 19 volumes of oxygen per 100 cc. It gives up, let us say, 6 volumes to the tissues, i.e., the mixed venous blood coming to the lungs contains 13 volumes per cent. The total quantity of oxygen consumed per minute is say 250 cc. Then the cardiac output is—

(Total O₂ consumption) (Output per minute)

$$\frac{250}{19 - 13} \times 100 = 4.16 \text{ liters}$$

(Arterio-venous O₂ difference)

The output can be calculated in a similar way from the total carbon dioxide elimination and the arterio-venous carbon dioxide difference (CO₂ in mixed venous blood less CO₂ in arterial blood). The total oxygen consumption (or carbon dioxide elimination) can be readily determined (p. 527).

The arterial oxygen or carbon dioxide content can be obtained by analyzing a sample of blood, or the quantity of either gas in the arterial blood can be calculated from their tensions. The latter, in turn, can be determined from an analysis of the alveolar air. It is difficult, on the other hand, to obtain the oxygen or carbon dioxide content of the *mixed venous blood* and several procedures have been devised for the purpose. It is not permissible simply to take the gas content of the blood in an arm vein since this is not equal to that of the mixed venous blood as it reaches the lungs. In animals the oxygen or carbon dioxide content of arterial blood and of mixed venous blood can be obtained by puncturing, respectively, the left and right sides of the heart. Such a method is usually unjustifiable in the case of the human subject owing to the risks involved, though it is sometimes employed (p. 231).

The method of Douglas and Haldane based upon the CO₂ arterio-venous difference

The CO₂ tension of the arterial blood is obtained from the tension of CO₂ in the alveolar air. The CO₂ tension of the mixed venous blood is obtained by breathing air mixtures containing different percentages of CO₂ from a series of bags, and holding the breath for a sufficient time to allow the mixture in the lung-bag system to come into equilibrium with the venous blood. That gas mixture of which two samples taken a short interval apart have practically the same CO₂ percentage is assumed to be in equilibrium with the venous blood. The whole procedure must not take longer than the time of a single circulation (20 seconds), i.e., the blood which has left the lungs must not be allowed time to return before the second sample is obtained, otherwise the CO₂ tension of the mixed venous blood would be raised artificially as a result of the absorption of CO₂ from the air mixture, and the results be vitiated. That is, the calculated CO₂ content of the mixed venous blood would be too high and the value for the cardiac output, in consequence, too low. Blood passes through the coronary circuit in about 10 seconds so the value for the cardiac output does not include the blood of the coronary system.

Three (or four) bags of 30 liters capacity are first filled with mixtures of air and CO₂. The respective mixtures are made up with proportions of CO₂ which increase in successive bags by 0.5 per cent. Thus, the mixture in bag number one contains approximately 6.5 per cent CO₂; bag two, 7.0 per cent; bag three, 7.5

per cent. The subject makes a maximal expiration into room air and then a maximal breath is taken from bag one. These two respiratory movements are repeated three times in order to ensure thorough mixing in the lungs, and to wash out the alveoli with the gas mixture in the bag. Each expiration is made into room air and each inspiration is taken from the bag. After the final inspiration the breath is held for 2 seconds and then a sharp partial expiration (of about 1600 cc.) is made down the Haldane alveolar-air tube (p. 311) and a specimen taken for CO₂ analysis. Due to the dilution with the lung air (which has a lower CO₂ percentage) this sample will be lower in CO₂ than that of the original bag mixture. The subject continues to hold his breath after this short expiration, and 6 seconds later a full expiration is made in order to expel the remainder of the air from the lungs. A second sample is taken for analysis. If this should show the same CO₂ percentage as the first it would then be inferred that in the interval the venous blood had neither given up nor absorbed any CO₂ from the lungs. In other words, the venous blood and alveolar air would be in equilibrium, and the tension of the CO₂ in the sample the same as that of the venous blood. Usually, however, the second analysis gives a higher value; CO₂ must have been given off by the venous blood, and the CO₂ tension of the latter is, therefore, higher than that of the mixture in bag 1. The same procedure is then repeated with the richer mixture in bag 2 (7.0 per cent CO₂). The second of the two analyses may still be higher than the first. If so, the third bag is employed when the second sample will either be the same or slightly lower than the first sample. The venous CO₂ tension in the latter case would be between that of the second samples of the second and third observations. On the other hand, if after breathing from bag 2 the second sample has a lower CO₂ percentage than has the first, CO₂ must have passed from the lungs to the venous blood (see table 19). With the use of the third bag (7.5 per cent CO₂) the second sample will also be lower, but the difference between it and the first sample will be greater than when the mixture in bag 2 was employed. This method of "straddling" shows that the gas mixture which would be in equilibrium with the venous blood must have a CO₂ percentage somewhere between those of the second samples in the first two observations (between 6.40 and 6.63 per cent in table above). A mixture having this percentage of CO₂ is then employed. When this is inspired and the usual procedure repeated, it is to be expected that there will be practically no difference between the first and second alveolar air analyses.

The CO₂ tension of the mixed venous blood is readily calculated from the CO₂ percentage of the gas sample in equilibrium with it (p. 315). The volumes per cent of CO₂ in the arterial blood and in the mixed venous blood are then obtained from the CO₂ dissociation curve, the lower (oxygenated) curve being employed for this purpose (p. 338).

The total CO₂ elimination per minute is determined

just before the re-breathing procedures by the Douglas bag method (p. 529). Then, if the total CO₂ elimination is, say, 208 cc. per minute and the arterio-venous CO₂ difference is 5 volumes per cent.

$$\frac{208}{5} \times 100 = 4.16 \text{ liters, cardiac output per minute.}$$

METHODS INVOLVING THE USE OF A FOREIGN GAS

Nitrous oxide (N₂O) and *ethyl iodide* (C₂H₅I) have been employed in the past. A method involving the use of *acetylene* (C₂H₂) was introduced in 1929 by Grollman. This gives the most accurate results and has largely superseded the older methods.

If a subject breathes an inert foreign gas (i.e., one which becomes dissolved in the plasma but does not combine with the hemoglobin, lipid or other constituents of the blood) and the quantity which has been absorbed in a given time be known, as well as the coefficient of solubility of the gas in plasma, then the quantity of blood which has

TABLE 19

	CO ₂ PER CENT AIR IN BAG	CO ₂ PER CENT IN ALVEOLAR AIR		PRESSURE OF CO ₂ IN VENOUS BLOOD IN RELATION TO ALVEOLAR AIR
		First sample	Second sample	
(1)	6.50	6.38	6.40	+
(2)	7.00	6.68	6.63	—
(3)	7.50	6.87	6.73	—

passed through the lungs can be calculated. This, in general, is the principle upon which the acetylene or any other foreign gas method is based.

The acetylene method. The subject rebreathes a mixture of acetylene (20 to 25 per cent) and air from a rubber bag (3 liters capacity) until the *lung-bag system* contains a homogeneous mixture. A sample of the mixture is taken and the percentages of acetylene, nitrogen and oxygen determined. The subject continues to rebreathe for 5 seconds. A second sample is then taken for analysis. The entire rebreathing procedure should not exceed the time of a single circulation (20 seconds) in order that no acetylene shall be returned to the lungs, and also that the arterio-venous oxygen difference shall not be altered from that existing prior to the rebreathing period.

The volume of the lung-bag system is reduced during the interval between the taking of the two samples, since the volumes of acetylene and oxygen absorbed are together greater than the carbon dioxide eliminated. Inasmuch as nitrogen takes no part in the respiratory exchanges, an increase in its percentage will be pro-

portional to the reduction of the volume of the mixture in the lung-bag-system. The relative gas volumes in the system at the times of the first and second samples, which may be designated V_I and V_{II} respectively, are therefore calculated from the nitrogen percentages at these times, $V_I:V_{II}::N_{II}:N_I$.

If $(C_2H_2)_I$ and $(C_2H_2)_{II}$ be used to designate the percentages of acetylene in the first and second samples, respectively, then the relative volumes of acetylene in the samples will be $V_I(C_2H_2)_I$ and $V_{II}(C_2H_2)_{II}$; and the volume of acetylene absorbed will be $V_I(C_2H_2)_I - V_{II}(C_2H_2)_{II}$. Knowing the average concentration of acetylene—

$$\frac{(C_2H_2)_I + (C_2H_2)_{II}}{2} = (C_2H_2)_{aver.}$$

in the lung-bag system in the interval between the taking of the two samples, and the coefficient of solubility of the gas, then the quantity absorbed per liter of blood is,

$$\frac{740 (C_2H_2)_{aver.}}{100} \times \frac{B - 48.1}{760}$$

740 = the number of cubic centimeters of acetylene which are dissolved by 1 liter of blood at body temperature when the tension of the gas is 760 mm. Hg
B = barometric pressure
48.1 = tension of water vapor in the lungs

Then:

Quantity of C_2H_2 absorbed during observation
Quantity of C_2H_2 absorbed per liter of blood

$$= \frac{[V_I(C_2H_2)_I - V_{II}(C_2H_2)_{II}] \times [760 \times 100]}{740 (C_2H_2)_{aver.} \times (B - 48.1)}$$

= Blood flow through lungs, i.e., cardiac output during rebreathing

The blood flow through the lungs, thus obtained, is affected by the experimental procedure itself, namely, the rebreathing. In order to obtain the cardiac output for the period immediately preceding the rebreathing period, the arterio-venous oxygen difference and the total oxygen consumption must be determined. Now, the arterio-venous oxygen difference during the actual experiment will be the same as that immediately preceding the period of rebreathing since this is shorter than the time of a single circulation. The oxygen absorption during the rebreathing period is obtained in a manner analogous to that by which the acetylene absorption is obtained. The volume of oxygen absorbed divided by the quantity of blood in liters passing through the lung during rebreathing gives the arterio-venous oxygen difference i.e., the quantity of oxygen absorbed by each liter of blood during its passage through the lungs. Thus—

Arterio-venous oxygen difference

$$\begin{aligned} &= \frac{[V_I(O_2)_I - V_{II}(O_2)_{II}] \times 740(C_2H_2)_{aver.}(B - 48.1)}{[V_I(C_2H_2)_I - V_{II}(C_2H_2)_{II}] \times [760 \times 100]} \\ &= \frac{(O_2)_{diff.} (C_2H_2)_{aver.} \times (B - 48.1) \times (0.00974)}{(C_2H_2)_{diff.}} \end{aligned}$$

The factor 0.00974 is derived by combining the constants 760 and 100, and 740,—

$$\left(\frac{740}{760 \times 100} = 0.00974 \right)$$

The total oxygen consumption is determined in the usual way just prior to the commencement of the rebreathing period. Then

Total O_2 consumption
Arterio-venous oxygen difference

= cardiac output in liters per minute

PHYSICAL METHODS

The *ballistocardiographic method* was originated by Henderson some years ago and has been elaborated and modified in recent years by Starr and his colleagues. The cardiac output is calculated from the record made by the recoil of the body caused by movements of the heart and blood in the opposite direction during systole. It involves the basic principle that "every reaction has an opposite and equal reaction." The apparatus or ballistocardiograph consists of a table suspended from the ceiling by wires and braced to prevent any but a horizontal movement in the long axis of the body. The patient lies supine on the table with his feet braced against a footboard. The movements of the table are opposed by a strong spring and magnified some 8,000 times through an optical recording system. The apparatus is calibrated by subjecting the table to a static force of 280 grams which causes the displacement by 1 cm. of the spot of light on the photographic surface. The normal ballistocardiogram shows three principal waves H, I, and J, inscribed during systole. Wave H is due to a small headward movement of the body and is caused by the movement feetward of the heart and of the blood within it, in the isometric period of systole (fig. 101 A). Wave I is due to a sharp recoil of the body feetward due to the ejection of blood into the aorta. The J wave is the result of a headward movement caused by the recoil of the aorta as the blood flows down the descending aorta. The stroke volume is calculated from the height of the waves, I and J, and by applying the following formula.

$$\text{Stroke volume} = 7\sqrt{[I + J]AC^{2/3}}$$

where A is the diameter of the aorta (calculated from age and surface area according to Bazett's data) and C the duration of the cardiac cycle; the minute volume is

obtained by multiplying the value of the stroke volume by the pulse rate.

Measurements of the cardiac output by the direct Fick method, which consists of sampling the mixed venous blood of the right auricle by means of a catheter introduced through an arm vein and of the arterial blood by arterial puncture, give values 18.5 per cent higher than those obtained by the ballistocardiographic method as just described, but when the figure for aortic cross section is obtained by a roentgenological method this difference is reduced to 3.5 per cent (Cournand and his associates).

The blood pressure method (as employed by Bazett and his associates). The stroke volume of the heart can be calculated if the following are known; (1) the volume

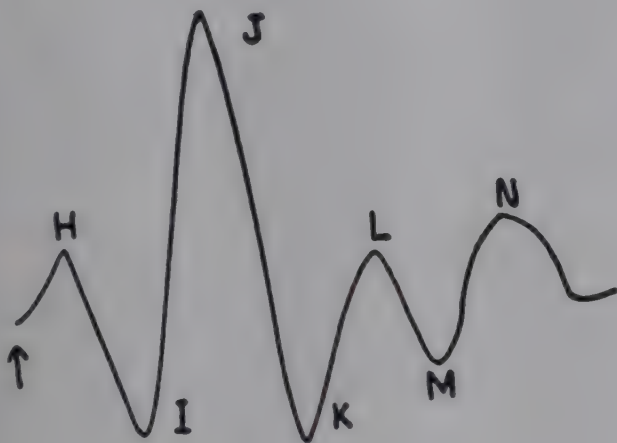


FIG. 101A

of the arterial vessels at the end of diastole, (2) the outflow from the arterial system during the cardiac cycle and (3) the distensibility of the arterial walls. The volume of the arterial system is calculated in sections—from commencement of aorta to the third part of the subclavian artery (\bar{V}_1) the descending aorta, with its iliacs and other branches except those nearer the heart than the subclavians (\bar{V}_2), the sections between the subclavian and the brachial at the elbow and including the other vessels of the upper part of the body with the same pulse wave velocities (V_3) and finally, the vessels of the lower limbs together with the vessels of the arms, splanchnic area and elsewhere having similar pulse wave velocities (\bar{V}_4). The values for \bar{V}_1 and \bar{V}_2 are obtained from tables giving the measurements in cadavers of different heights, surface areas and ages. The volumes \bar{V}_3 and \bar{V}_4 are assumed to vary with size of body but not with age, and are purely empirical, being

based upon the ability of the equations to give results which agree with those obtained by the acetylene method.

The distensibility of the arterial walls is determined from the pulse wave velocities (p. 150) in the different sections, recording tambours being placed upon the apex beat, subclavian, brachial, femoral, and dorsalis pedis arteries.

The outflow during diastole is determined from the change in volume of the arterial vessels from the peak of the diastolic wave to the end diastole. The volume change is estimated, in turn, from Bramwell and Hill's modification of Moen's equation, namely, *that the percentage of volume change per millimeter of mercury*

increases in pressure = $\frac{12.7}{v_1}$ where v_1 is the pulse wave velocity in meters per second. The outflow from the arterial system during diastole is then calculated from the equation

$$V_d = \frac{12.7(Z - D)}{100} \left(\frac{\bar{V}_1}{v_1^2} + \frac{\bar{V}_2}{v_2^2} + \frac{\bar{V}_3}{v_3^2} + \frac{\bar{V}_4}{v_4^2} \right)$$

where V_d is the outflow of blood during diastole, Z the diastolic pressure, and D the pressure at the end of diastole, V_1 to V_4 the volumes of the arterial sections already described and v_1 to v_4 the pulse wave velocities in these sections.

The outflow during systole (s period) must, of course, be taken into account. It is related to and derived from the volume leaving in the diastolic period (V_d) and calculated from the ratio of the mean pressures in the two periods. Thus,

$$V_s = V_d \times s/d \left(\frac{M_s - a}{M_d - a} \right)$$

where V_s is the volume of blood leaving the arterial system during systole, M_s and M_d are the mean pressures during systole and diastole; a is a constant having usually a value of 20 when the blood pressure is expressed in millimeters of mercury. The *stroke volume* (V) = $V_s + V_d$ and the *output of the heart per minute* (V_1) = $V \times F$, where F is the pulse rate.

The results of this method have been found to agree within less than 10 per cent with those of the acetylene method.

CHAPTER XXVII

THE CONTROL OF THE BLOOD VESSELS. THE VASOMOTOR MECHANISMS. PERIPHERAL VASCULAR DISORDERS. SURGICAL SHOCK.

The walls of the arterioles are composed chiefly of involuntary muscle fibers arranged in a circular fashion. Like the cardiac muscle the musculature of these vessels is supplied by two types of nerve fibers—inhibitory and excitatory. Those which cause contraction of the arteriolar musculature are called *vasoconstrictor*; those which inhibit, and in consequence cause relaxation of the muscular rings, are termed *vasodilator*. The former are therefore analogous to the cardiac accelerator (augmentor) nerves, and the latter to the vagi. Both sets together are referred to as the *vasomotor nerves*.

THE VASOCONSTRICTOR FIBERS

These were discovered in 1852 by Claude Bernard, who stimulated the cervical sympathetic nerve in the rabbit and observed constriction of the vessels of the ear. They belong to the thoraco-lumbar (sympathetic) division of the involuntary nervous system. The constrictor fibers arise from groups of nerve cells situated in the lateral horns of the cord, extending in man from the first thoracic to the second or third lumbar segment, inclusive. All the arterioles of the body wherever situated are supplied with filaments whose ultimate source is in this relatively limited region of the central nervous system. They are distributed to the periphery in the manner elsewhere described for the thoraco-lumbar outflow in general (see p. 936).

The vascular nerves of the limbs, as shown by Todd and Kramer and by Woollard, are distributed by two distinct modes. (1) A *proximal* innervation which arises in the case of the vessels of the upper limb directly from the cervical part of the sympathetic chain—middle and inferior cervical ganglia. The fibers pass to the subclavian artery and are conveyed in a plexiform manner along the outer coat of this vessel and its branches, and into the arm along the axillary artery. The corresponding supply to the vessels of the lower limb is derived by extension from the aortic plexus in the abdomen. The fibers follow the common and external iliac arteries into the thigh. The sympathetic fibers derived in the manner just de-

scribed do not extend beyond the larger vessels of the limbs—proximal portions of the brachial and femoral. (2) A *distal* innervation which is carried to the peripheral vessels via the somatic nerve trunks (e.g., ulnar, sciatic, etc., fig. 102). These reach the arteries at different levels and, penetrating the vascular wall, form a nerve net surrounding the muscular coat; the highest level of this type of innervation probably overlaps the region innervated by the proximal group of fibers mentioned above. The lowest levels supply the arterioles and capillaries. It is solely through such sympathetic fibers traveling with somatic nerve trunks that constrictor impulses are conveyed to the minute vessels of the limbs. Ganglion cells are absent from the vessels of the limbs. Section of a peripheral nerve, therefore, causes complete degeneration of vasoconstrictor fibers in the area of its distribution.

The existence of the distally distributed set of vasoconstrictor fibers has an important bearing upon operations designed to denervate the vessels. Periarterial neurectomy, for example, in which a segment of a main artery is stripped, will interrupt fibers belonging to the proximal set but will leave the distal supply to the vessels intact. Histological examinations of the peripheral vessels of limbs which had been amputated some time after periarterial neurectomy had been performed have shown only undegenerated nerve filaments.

Vasoconstrictor fibers to the head and neck are conveyed from the sympathetic chain through plexuses investing the blood vessels, but also via peripheral nerve trunks (cervical and certain cranial nerves). The vessels of the abdomen and pelvis are supplied with fibers which pass along the vascular walls from plexuses surrounding the aorta and its branches.

The vasoconstrictor fibers are non-medullated, but other fine medullated fibers may be detected ramifying around the peripheral vessels. These are afferent and convey sensory impulses (pain) from the vessels as well as dilator impulses (antidromic, p. 235) to the vascular muscle; they travel in the mixed somatic nerves and enter the cord

by the posterior spinal nerve roots. None degenerates after removal of the sympathetic chain.

Evidence has accumulated within recent years which indicates that vasoconstrictor, like certain

THE VASODILATOR FIBERS

The origins of the vasodilator fibers are more diverse than those of the vasoconstrictors. Dila-

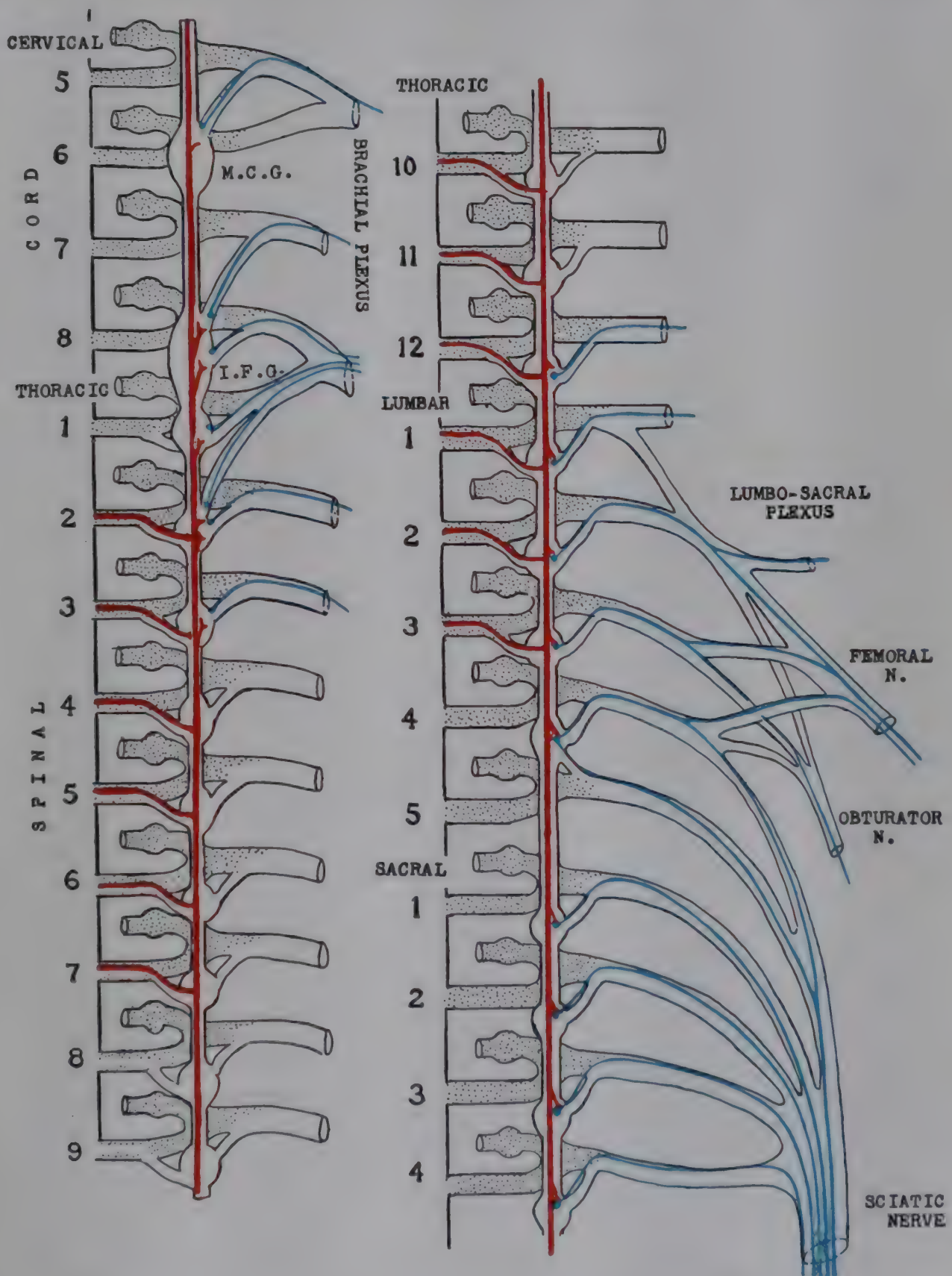


FIG. 102. Origin of the vasoconstrictor fibers to the limbs and their distribution in the peripheral nerves. M.C.G., middle cervical ganglion; I.F.G., inferior cervical ganglion. Superior cervical ganglion and distribution of vasoconstrictors to head are not shown (see also p. 938). Preganglionic fibers, red; postganglionic, blue.

other sympathetic effects, are mediated through the liberation of an adrenaline-like substance at the nerve endings (see pp. 212, 691 and 946).

tor impulses emerge from the central nervous system by: (1) the *thoracico-lumbar outflow* the fibers of which reach a given vascular area by the

same route as that travelled by the vasoconstrictor impulses, (2) the *cranial outflow* of the parasympathetic division reaching the periphery via the *chorda tympani*, *glossopharyngeal* and the *vagus* nerves, (3) the *sacral outflow or pelvic nerve*, and (4) *the posterior spinal nerve roots—antidromic impulses*.

VASODILATORS OF THE THORACICO-LUMBAR DIVISION
(SYMPATHETIC)

The question of vasodilator fibers in the sympathetic has been debated, since most workers in the past doubted their existence. Several observations had, nevertheless, suggested such a distribution. Dastre and Morat, for example,

the dilators had apparently been unmasked when the stronger vasoconstrictor effect was annulled by the drug.

Burn produced further evidence for the presence of vasodilators in the lumbar sympathetic chain of the dog. After the blood pressure had been elevated (by the infusion of adrenaline) stimulation of this nerve caused vasodilatation and a fall in blood pressure.

The sympathetic vasodilators are of two types, namely, those which bring about their effect by the liberation of acetylcholine (*cholinergic fibers*, p. 950) and those whose action is mediated by an adrenaline-like substance (*adrenergic fibers*). The distribution of each type varies with the species and in different vascu-

TABLE 20
Distribution of vasoconstrictors (see also Chapter LXXIII)

REGION OF BODY	ORIGINS	
	Preganglionic fibers	Postganglionic fibers
Head	1st and 2nd thoracic segments of cord (man)	Superior cervical ganglion
Upper limb and neck .	3rd to 7th thoracic segments inclusive (man)	1st, 2nd and 3rd thoracic and inferior and middle cervical ganglia thence via nerves of brachial plexus
Lower limb	10th thoracic to 2nd lumbar segments	From 12th thoracic to 4th sacral ganglia thence via nerves of lumbo-sacral plexus
Thoracic aorta and branches	1st to 5th thoracic segments	Middle and inferior cervical and 1st to 5th thoracic ganglia
Pulmonary vessels . . .	2nd, 3rd and 4th thoracic segments	
Abdominal and pelvic viscera	6th thoracic to 3rd lumbar segments inclusive	Celiac, mesenteric and hypogastric ganglia (no cell stations on vertebral chain of ganglia)

observed flushing of the buccal mucosa upon stimulation of the cervical sympathetic; this observation was confirmed by others (Carlson, Langley). The phenomenon, however, was ascribed by Gaskill, Bayliss and others not to vasodilator impulses but to the liberation of vasodilator substances (CO₂, lactic acid, etc.) from neighboring small glands of the mucosa, excited by the stimulation of secretory fibers contained in the cervical sympathetic.

On the other hand, Dale showed that after ergotoxine, which abolishes secretory as well as vasoconstrictor and other motor sympathetic effects, stimulation of the splanchnic or of the abdominal sympathetic caused dilatation of the vessels of the intestine or of the leg, respectively. This was strong evidence for the existence of sympathetic vasodilator fibers. The action of

lar areas of the same species. In the dog and hare the muscles are plentifully supplied with sympathetic vasodilators of the cholinergic variety (Bülbring and Burn). Stimulation of sympathetic fibers to the muscle vessels of the dog after ergotoxine administration (which paralyses constrictor fibers) causes vasodilatation, the reaction being enhanced by eserine (physostigmine) and abolished by atropine. Moreover, a vasodilator response is obtained from the stimulation of sympathetic fibers if eserine has been administered previously, the action of the vasodilators now overbalancing that of the constrictors. There are only a few sympathetic vasodilators in the muscles of the cat and they are entirely adrenergic, the vasodilation caused by stimulation of the sympathetic after ergotoxine administration being unaffected by eserine or atropine. That cholinergic sympathetic vasodilators also innervate some vascular area in the cat is indicated by the experiments of Cannon and Rosenblueth who found that the

fall in blood pressure following stimulation of the abdominal sympathetic after ergotoxine was enhanced by eserine and reduced or abolished by atropine. The muscles of the monkey and of the rabbit receive no sympathetic vasodilator fibers of either kind. The skin of the dog, except over the ears, is devoid of sympathetic vasodilators. The presence of sympathetic vasodilators in the human skin is in dispute. The experiments of Lewis and Pickering seemed to have demonstrated the existence of such fibers, but Uprus, Gaylor and Carmichael in a later investigation have questioned the conclusions of the previous workers (see, however, Fatheree and Allan for affirmatory evidence).

ANTIDROMIC VASODILATOR IMPULSES

Stricker many years ago (1876-1877) reported that stimulation of the peripheral segments of the cut posterior roots of the sacral nerves caused dilatation of the vessels of the hind paw of the dog. This observation was at variance with the Bell-Majendie law which states that the posterior roots convey only centripetal impulses. Stricker's results were, consequently, not generally accepted. The question was studied afresh by Bayliss who showed in a series of carefully controlled experiments that Stricker's observation was essentially correct. Stimulation of the distal cut ends of the posterior roots of the 4th lumbar or the 1st sacral nerve, for example, was followed in every instance by dilatation of the vessels of the hind limb. Electrical, thermal and, especially, mechanical stimuli were effective. The effectiveness of the latter type of stimulus, which can be strictly localized, showed that the dilator response was actually due to the stimulation of posterior root fibers and not to the inadvertent stimulation of the anterior roots, as might occur with the use of an electrical type of stimulus (as a result of the escape of current). Furthermore, dilator effects in the vessels of the hind limb could be produced by stimulating the central end of an afferent nerve (such as the cardiac depressor, p. 240) after the abdominal sympathetic chain had been excised. This experiment shows that fibers of the posterior roots constitute the efferent limb of a depressor reflex.

There still remained the possibility, nevertheless, that *efferent fibers*, leaving the cord in the posterior roots, and not the ordinary sensory fibers were responsible for the dilator effect. Such a possibility was excluded, however, by sectioning the root between the ganglion and the cord and allowing time for degeneration to take place. Any efferent fibers would be cut off from their nerve cells by this operation and must, therefore, undergo degen-

eration. Afferent fibers, on the contrary, being still in connection with the cell bodies in the root ganglion would survive. Following the period allowed for degeneration, stimulation of the peripheral segment of the sectioned root caused the usual vasodilator response. On the other hand, when the section was made *distal* to the ganglion, stimulation of the distal stump after degeneration of the sensory fibers had occurred failed to cause vasodilatation. Trophic centers for the vasodilator fibers must, therefore, lie in the posterior root ganglia. The application to the ganglion of nicotine, which acts upon the synaptic junctions, did not abolish the vasodilator response when the posterior root was simulated on the central side of the ganglion. This fact indicates that the dilator fiber does not synapse within the ganglion. All the evidence points to the vasodilator fibers being derived from the ordinary bipolar ganglion cells, i.e., that they are identical with the afferent fibers of the peripheral nerves and posterior roots. In other words, the vasodilator impulses are conveyed along the fiber in a direction opposed to that in which the ordinary sensory impulses travel. For this reason they have been termed *antidromic* (running against) by Bayliss and Langley. Sherrington, from histological evidence, had also concluded that the posterior roots were free from efferent fibers. He sectioned the roots in monkeys and cats proximal to the ganglia and, after time had been allowed for degeneration to occur, examined the peripheral stumps for degenerated fibers; none was found.

Foerster, more recently, obtained cutaneous vasodilatation in man by stimulation of the posterior nerve roots at various levels of the cord. The vasodilatation had a segmental distribution.

According to Bayliss and Head, the sensory fibers which transmit the vasodilator impulses are those which subserve the sensation of pain (protopathic) and it was shown by Bayliss that in the case of the limb the antidromic impulses pass mainly to the vessels of the skin, few, if any, to vessels of the muscles. It appears that the vasodilator fibers of the posterior roots are distributed mainly if not entirely to the cutaneous and visceral vessels (the fibers to the latter travelling in the splanchnics). Bayliss observed that the limb deprived of skin showed only a slight increase in volume after stimulation of the appropriate posterior roots. The dilators to the vessels of skeletal and cardiac muscle, on the other hand, are derived from the sympathetic

(pp. 234 and 278). The vessels of skeletal muscle are therefore dependent upon the sympathetic for the transmission of both dilator and constrictor impulses. As compared with the skin and viscera, however, the muscular vessels rely to a greater extent upon metabolic products, carbon dioxide and lactic acid, for the control (p. 248) of their calibers. The vasodilatation which occurs in glands accompanying their secretion is also probably to a large extent due to the direct action of metabolites upon the vascular walls.

Antidromic vasodilator fibers homologous with those of the posterior roots are believed to exist also in certain cranial nerves, e.g., the trigeminal, which carried dilator impulses to the face and tongue (lingual). The conception of an antidromic vasodilator mechanism has far-reaching implications and has helped very greatly toward an understanding of several clinical phenomena hitherto inexplicable. Of these may be mentioned the vascular changes in certain diseases affecting the sensory side of the nervous system and the cutaneous lesions arising in tabes, especially along the course of the lightning pains. The blisters which occur in herpes zoster have been shown by Head and Campbell to be associated with lesions of the cells of the posterior nerve roots.

Within recent years the question of antidromic transmission of vasodilator impulses has been questioned by some observers who claim to have demonstrated the presence of efferent fibers in the posterior roots. The Japanese school, headed by Ken Kure, has referred to these fibers as constituting a "spinal parasympathetic system." This conception has not gained general acceptance. Quite recently, however, Kahr and Sheehan obtained evidence for the existence of efferent fibers in the posterior roots of cats. When the posterior roots from 12 thoracic to 2 lumbar were sectioned between the ganglion and the cord and time allowed for degeneration to occur, undegenerated fibers were found in the proximal stumps and degenerated fibers in the distal stumps. These, it was concluded, must have been derived from nerve cells situated within the central nervous system, and studies of sections of the cord revealed changes in the Nissl bodies of cells situated in the lateral and anterior horns ("retrograde" degeneration, p. 779). But, though the existence of efferent fibers in the posterior roots should be demonstrated conclusively by histological methods, it does not necessarily follow that they convey vasodilator impulses. The physiological experiments of Bayliss cited above furnish strong evidence that vasodilator impulses are transmitted antidromically in the posterior roots. Even if efferent fibers made connection with cells in the root ganglia (as is maintained by Kure, but which remains unproved) Bayliss' experiments could be ex-

plained, only in part, otherwise than by the antidromic hypothesis. Nevertheless, the conception of antidromic impulses has been a difficult one for physiologists to accept because it contradicts the Bell-Magenau law (p. 810). It is not possible to discuss the question here except in the most cursory manner. The reader is referred to a paper by Bishop and associates and to a recent article by Barron and Matthews. The former observers consider that the vasodilator fibers of the posterior roots, though having their cell stations in the posterior roots are efferent in function, and analogous to similar fibers in the vagus. Barron and Matthews find that certain fibers of the posterior roots, which from degeneration experiments apparently have their trophic centers within the cord, are in reality derived from posterior root ganglia situated at a lower level. That is, the sensory fiber after entering the cord and ascending for a short distance gives off collaterals which emerge in the posterior root of a higher spinal segment. When the posterior root is sectioned between the posterior root ganglion and the cord these collateral fibers must, of course, undergo degeneration distal to the point of section. The presence of such fibers may explain the findings of Kahr and Sheehan mentioned above. It is clear that the results of further investigation alone can lead to a complete elucidation of the nature of the vasodilator fibers in the posterior roots.

THE PELVIC NERVE (NERVUS ERIGENS) AND THE PHENOMENON OF ERECTION

The pelvic nerve is composed of fibers which leave the cord in the anterior roots of the 2nd, 3rd and sometimes the 1st and 4th sacral nerves. It conveys dilator fibers to the vessels of the penis or clitoris. The erectile tissue of these organs is composed of cavernous blood sinuses whose walls contain involuntary muscle. To reach these spaces the blood passes through arterioles and capillaries. The outlets from the sinuses are guarded by rings of involuntary muscle. Dilator impulses cause arteriolar and capillary dilatation coincident with inhibition of the involuntary muscle in the walls of the sinuses, and excitation of the muscle guarding their outlets. These effects cause dilatation of the vascular spaces, a high pressure within them, and, as a consequence, hardening and erection of the organ. There is also evidence that arterio-venous anastomoses (p. 273) also exist which open up to increase the blood flow into the erectile tissue. The narrowing of the venous outlets impedes the outflow from the sinuses only until the blood pressure within their cavities is raised to a certain height; then the outflow from the organ equals the inflow and the velocity of flow through the erectile tissue becomes greatly increased. This is evidenced by

rise in temperature and the bright arterial color of the blood flowing along the dorsal vein of the penis. The arterioles, capillaries and walls of the sinuses are also furnished with constrictor fibers, derived from the prostatic plexus (p. 941); stimulation of these nerves by reducing the blood flow through it cause shrinkage of the organ. The afferent pathway for the reflex of erection is through the pudendal nerves.

The constrictor center, occupies the apex of the ala cinerea or the fovea inferior. The second point—the vasodilator center—lies just lateral to the obex. Both centers are bilaterally represented. It is unlikely that these areas represent the highest centers of the vasomotor system. More recent work indicates that the latter are situated in the hypothalamus, and even in the cerebral cortex.

TABLE 21
Summary of vasodilator fibers (see also Chapter LXXIII)

REGION	ORIGIN	COURSE
	Parasympathetic (cranial outflow) Thoracico-lumbar outflow	7th, 9th and 10th cranial nerves. Cervical sympathetic cord
limb.....	6th, 7th, 8th cervical and 1st thoracic segments Thoracico-lumbar outflow probably from same segments as those giving rise to constrictors (p. 900)	Posterior roots of corresponding somatic nerves Probably same as vaso-constrictors
limb.....	5th, 6th and 7th lumbar 1st and 2nd sacral Thoracico-lumbar outflow probably from same segments as those giving rise to constrictors	Posterior roots of corresponding somatic nerves Abdominal sympathetic chain and somatic nerves
abdominal and pelvic organs.....	Thoracico-lumbar outflow probably from same segments as those giving rise to constrictors	Splanchnics
or clitoris.....	Parasympathetic (sacral outflow) 2nd, 3rd and 4th sacral segments	Anterior roots and nervi erigentes (pelvic nerves)

The pelvic nerve also sends dilator fibers to the walls of the rectum, descending colon and bladder.

THE VASOMOTOR CENTERS

The constrictor and dilator vascular effects are controlled by centers—the vasoconstrictor and vasodilator centers—situated in the floor of the 4th ventricle of the medulla. The constrictor center is also connected to a subsidiary center (or group of centers) in the cord. This is constituted of the cells in the thoracico-lumbar region of the medulla already mentioned (p. 232). Ranson and Langley explored the floor of the 4th ventricle by means of a needle electrode and located two points which when stimulated caused respectively a rise or a fall in blood pressure of from 30 to 40 Hg. The former point, which probably

VASOMOTOR TONE AND ITS REGULATION

The constrictor center exhibits tone. It is generally stated that dilator tone is absent, but Bayliss has shown that this exists to a slight degree, under certain circumstances at any rate. Dilator tone is much more difficult to demonstrate since constrictor and dilator fibers in most instances run together and the effects of the former mask those of the latter. The tone of the vasoconstrictor center may be demonstrated by sectioning the cord in the lower cervical region. This interrupts the stream of impulses passing from the medullary to the spinal centers, the vessels dilate and the blood pressure falls. After a time, however, the blood pressure rises again; the spinal centers exhibit their inherent power of autonomous action, and assuming the duties hitherto exercised

by the medullary centers, restore the vessels to their previous state of tonic constriction. The time required for the vessels to regain their tone after section of the cord varies considerably in different species (see spinal shock, p. 828).

The high degree of vasoconstrictor tone which is normally maintained is shown by the fact that section of the splanchnics doubles the flow in the vessels of the denervated area (Burton-Opitz). A corresponding increase in the flow through the femoral artery after removal of the lumbar sympathetic has been demonstrated by Herrick, Essex and Baldes; the greater flow persists for several months.

After the tone resulting from cord section has been restored it falls again if the splanchnics are sectioned, but after a time a certain degree of tone is regained. This resides in the vascular muscle itself—*peripheral tone*. Apparently, a long period is required for the development of the intrinsic arteriolar tone. Essex and his associates found that, nearly eleven months after its denervation, the flow in the dog's femoral artery was double that in the opposite femoral. But nine years after the operation, the flow was almost equal on the two sides. Examination of the small vessels of the denervated side showed pronounced hypertrophy of the muscular coat. The vessels of this side were also especially susceptible to the constrictor action of adrenaline (see p. 686).

The tone of the vasomotor center is dependent (1) upon afferent nerve impulses received from various organs and regions of the body as well as from other nervous centers (cerebral cortex, respiratory center etc., see p. 245) and (2) upon the chemical composition of the blood.

VASOMOTOR REFLEXES

Vasomotor reflexes can be elicited by the stimulation of practically any afferent nerve—somatic or visceral.

VASCULAR REFLEXES RESULTING FROM THE STIMULATION OF SOMATIC NERVES

Stimulation of the central end of a nerve such as the *sciatic*, the *median* or a sensory *cranial* nerve may result in either a rise or a fall in the arterial blood pressure according to the strength and type of the stimulus employed. An elevation or depression of the blood pressure brought about in this way is spoken of, respectively, as a *pressor* or a *depressor reflex*. The components of the reflex arc upon which the responses depend are, (1)

afferent fibers in the peripheral nerve, (2) the vasomotor centers, and (3) the efferent vascular nerves, i.e., the vasoconstrictors or vasodilators.

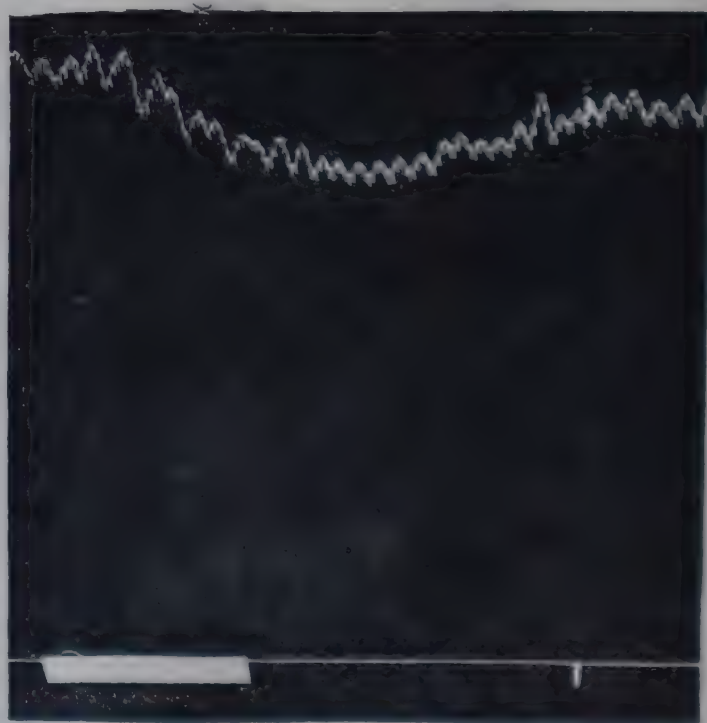


FIG. 103. Effect of stimulating somatic nerves upon arterial blood pressure. Upper tracing shows rise in carotid pressure during faradic stimulation of the central end of the brachial nerve of cat. Lower tracing shows fall in blood pressure as a result of stimulating the central end of the sciatic nerve. (After Ranson and Billingsley.)

In order to elicit the pressor reflex, a stimulus much stronger than that necessary to provoke the depressor response must, as a rule, be applied, that is, one which would elicit pain in a conscious animal. Stimulation of the cornea which is supplied liberally with pain fibers gives a definite pressor response. In a series of experiments by

Ranson and Billingsley, the pressor response ranged from 8 to 45 mm. Hg and the depressor from 4 to 22 mm. Hg (fig. 103). In the elicitation of either reflex the magnitude of the response is apparently dependent upon the number of afferent fibers involved. For example, stimulation of various nerves of the brachial or lumbar plexus caused practically equivalent depressions or elevations in the blood pressure when the number of afferent fibers in the respective nerves was taken into account. It has also been shown by Martin and Stiles that similar reflex effects evoked simultaneously from separate afferent nerves are summed; dissimilar reflexes are mutually antagonistic.

It has been thought that these contrary effects upon the blood pressure were dependent upon two corresponding types of specific afferent fibers—pressor and depressor—in the peripheral nerve. The fact that stimuli of different intensities and frequencies caused opposite effects seemed in itself to imply the presence of two sets of fibers, one with a higher threshold than the other. Weak, slowly repeated stimuli are more likely to cause a fall, strong rapidly repeated stimuli a rise in blood pressure. Other observations seemed to point to the existence of two separate sets of fibers. After cooling the nerve, or sectioning it and allowing a certain period to elapse, the depressor effect could be obtained but not the pressor. The pressor fibers were presumed to degenerate before the depressor. Again, depressor reflexes are obtained more readily from cranial nerves, whereas the usual response to stimulation of the central end of a spinal sensory nerve is a pressor response, which suggested that different nerves contain the respective types of afferent fibers in varying proportions. The work of Ranson and Billingsley indicates that the pressor fibers are not specific but are identical with those which subserve protopathic sensibility (pain, extremes of temperature, p. 803), whereas the depressor fibers correspond to those which transmit sensations of touch or warmth. According to Ranson the fibers transmitting *pressor* are unmyelinated and enter the cord in the lateral division of the posterior roots. Their intraspinal course is by short internuncial fibers in the tract of Lissauer, the nerve cells lying in the gray matter of the tip of the posterior horn. An experimental lesion, involving this pathway on both sides of the cord in the lumbar region or of the lateral divisions of the posterior roots, was shown by Ranson and his associates to abolish the pressor reflex usually obtained by stimulation of the sciatic. The depressor reflex remained unaffected. The intraspinal part of the *efferent* limb of the pressor reflex lies in the anterior or the lateral column of the cord. The impulses (vasoconstrictor), as mentioned elsewhere, leave the cord by the white rami. In support of the conclusion that the pressor fibers are identical with those mediating proto-

pathic sensibility, Bayliss and Head observed that after section of a peripheral nerve, the pressor reflex (but not the depressor) could be elicited from the regenerating nerve at the time when protopathic sensibility was returning. The association of pressor responses with painful sensations points to their being an integral part of the defensive mechanisms (nociceptive reflexes, adrenaline liberation, etc.).

After entering the cord by the posterior roots the *depressor* impulses ascend in that part of the lateral column occupied by the spino-thalamic tracts. But they are not identical with the fibers of the latter since they end in the medulla (vasodilator center). Bilateral section of this part of the lateral column abolishes the depressor reflex; the pressor reflex becomes more pronounced which suggests that ordinarily it contains a masked depressor element. The intraspinal *efferent* limb of the depressor reflex (vaodilator) is unknown.

It must be mentioned that not all the pressor or depressor impulses ascend to the medulla but that reflex arcs exist having their centers within the cord; both vasoconstrictor and vasodilator reflexes can be elicited in an animal whose cord has been divided in the lower cervical region a short time previously.

Pressor and depressor reflexes can be readily elicited in man by peripheral nerve stimulation. Warmth, for instance, applied to the feet or other part of the body causes vasodilatation in other parts remote from the point of application and a fall in pressure may result. If, however, the applied temperature is raised to the point where it becomes painful, reflex vasoconstriction occurs. The application of cold also usually produces the latter effect. The vasodilatation in one extremity resulting from the immersion of another in warm water is not due to the stimulation of afferent endings in the heated tissues, but to the warmed blood acting upon a nervous center; through this and the efferent nerves the vasodilatation is brought about. Gibbon and Landis, for example, showed that the vascular response was abolished by occluding the circulation of the heated member and that it could be produced in the hands of a subject with complete transection of the cord by warming the feet. The response to cold is due in part to afferent impulses and in part to the effect of the altered temperature of the blood returned from the cooled member upon the nervous center. A change in temperature (a rise or fall) of the tissues of from 0.01 to 0.04°C. is sufficient to induce the vascular response. Other interesting reflex vascular reactions must be mentioned. Mudd and Grant showed that a

draught directed to the bare back or arm caused constriction of the vessels of the pharynx and nasal mucosa. Constriction of the vessels of the bronchi as a result of the application of cold to a remote part of the body has also been observed by means of the bronchoscope. On the other hand, deep inspiration causes reflex constriction of the cutaneous vessels. From the results of experiments upon animals it is to be expected that in the human subject a painful stimulus applied to a somatic nerve will be followed by a pressor response. The excitation of psychic centers, and also the liberation of adrenaline are additional factors which play an important part in the pressor response resulting from painful stimuli. On the other hand, stimulation of the mesentery, peritoneum and abdominal viscera or of certain regions such as the anus, vagina and spermatic cord is usually followed by a fall in blood pressure. Bayliss demonstrated a fact of some practical importance, namely, that pressor reflexes become depressor in character under chloroform anesthesia; this reversal was not observed when ether was employed. Strychnine tended to annul the effect of chloroform and to convert depressor reflexes into those of the pressor type.

VASCULAR REFLEXES MEDIATED THROUGH AFFERENT FIBERS OF THE VAGUS

In the section dealing with the reflex control of the heart rate it was mentioned that the vagus contains afferent fibers which terminate in the aortic arch and heart. Stimulation of these fibers also produces alterations in the caliber of the blood vessels and, as a result, changes in blood pressure. In some instances, electrical stimulation of the cerebral stump of the severed vagus is followed by a rise in blood pressure (pressor reflex); more usually, however, a fall in pressure occurs (depressor reflex).

Vagopressor reflexes

The pressor fibers of the vagus are stimulated by a fall in the pressure of blood in the great veins emptying into the right auricle. McDowall, confirming an old observation of Pavlov's, found that when the venous pressure was lowered by hemorrhage (or by the intravenous injection of alcohol or of histamine) no change or a moderate decline in the arterial pressure occurred so long as the vagus nerves were intact. When, however, these nerves were severed, a fall in arterial pres-

sure occurred if this had been unchanged prior to the nerve section, or a further fall resulted if the arterial pressure had been already lowered coincidentally with the fall in venous pressure. These observations have been confirmed by Anrep and Segall. Cocainization of the auricle has the same effect as vagotomy. It is concluded from these results that the fall in venous pressure exerts an influence upon afferent vagal endings situated in the right auricle; messages ascend to the medullary centers and cause a generalized vasoconstriction. This reflex is probably responsible in part for the vasoconstriction which occurs as the usual response to hemorrhage and surgical shock (p. 258), both of which conditions are associated with a fall in venous pressure.

It has also been shown by McDowall that a rise in venous pressure considerably above the normal level calls forth a vagopressor reflex, as evidenced by the vasoconstriction which occurs in a limb connected to the body solely by its nerves, when saline is injected into the inferior vena cava. This reflex occurs coincidentally with and is supplementary to the Bainbridge reflex (cardiac acceleration, p. 209). It antagonizes the depressor reflex elicited from the aortic nerve or carotid sinus and McDowall suggests that through its predominance over the latter reflexes (see below) the elevation of the arterial pressure is permitted to persist throughout muscular exercise.

The aortic or cardiac depressor nerve

In certain animals (e.g., the rabbit) the vagal fibers mediating the depressor response of this nerve are collected into a separate nerve which arises from the trunk of the vagus high in the neck. This branch of the vagus which is known as the *aortic or cardiac depressor nerve* was first described by Cyon and Ludwig (1866). It is purely afferent and depressor in function; when sectioned and its central (cerebral) end stimulated a pronounced fall in pressure occurs (fig. 104); excitation of the cardiac end, on the other hand, causes no effect. Two factors are involved in the depressor response following stimulation of the depressor fibers (whether these are contained within the vagus itself or are segregated in the aortic nerve); (1) *slowing of the heart rate and increased force of the ventricular contraction*. The efferent fibers of the vagus of the same and of the opposite side constitute the efferent limb of the reflex arc through which this response is brought about (p. 205); for its elicitation at least one vagus must, therefore,

remain intact. (2) *Vasodilatation*. The vasomotor pathways constitute the efferent limb of this reflex. Vasoconstrictor tone is reduced and vasodilator tone increased. The reflex effect upon the vessels cannot, therefore, be elicited after section of the spinal cord in the lower cervical region.

The receptors of the reflex (i.e., the terminals of the aortic nerve) are situated in the aortic arch and upper part of the thoracic aorta, in the ventricles and probably also, according to Daly and Verney, in the coronary and pulmonary vessels (see fig. 106).

The fall in pressure is due mainly to dilatation of the splanchnic vessels. The dilatation is not, however, confined to these vessels but includes

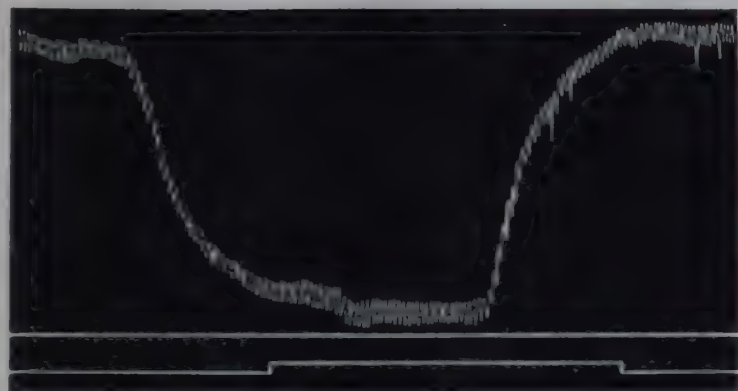


FIG. 104. Fall in arterial blood pressure resulting from stimulation of the central end of the cardiac depressor (aortic) nerve. The drum was stopped in the middle of the curve and the excitation maintained for seventeen minutes. The line of zero pressure should be 30 mm. lower than here shown. (From Bayliss.)

those of the skin and muscles. Cardiac slowing plays a minor rôle in the production of the fall in blood pressure, for almost as great an effect can be obtained after both vagi have been cut. The depressor reflex can be elicited by mechanical or electrical stimulation of the aortic wall itself wherein the special proprioceptors are located; stretching is an especially effective type of stimulus. It was also shown by Einthoven and subsequently by several other observers that action currents ascend the nerve synchronously with the heart beats. The normal stimulus is, therefore, quite evidently the pulsatile expansion of the aortic wall, a rise in general blood pressure increasing the intensity of the stimulus, a fall in pressure causing the reverse effect. A small structure (*glomus aorticum*) analogous to the carotid body (see footnote p. 242) is connected with a branch of a fine artery arising from the aorta beyond its arch. The chemoreceptors of this structure

respond to oxygen lack. Reflex vasoconstriction and a rise in blood pressure follow their stimulation by anoxemia or by such drugs as cyanide, lobeline, nicotine, sodium sulphide and acetylcholine.

THE CAROTID SINUS MECHANISM.

(SEE ALSO P. 346)

The carotid sinus is the term applied to the slight enlargement of the common carotid artery where it bifurcates into the internal and external carotids (fig. 105). The dilatation usually involves, as well, the commencement of the internal carotid, or may be confined to this region. The



FIG. 105. Showing the carotid sinus region in man (after Heymans). 1, common carotid; 2, carotid sinus; 3, internal carotid; 4, external carotid; 5, nerve to carotid sinus; 6, glossopharyngeal nerve.

carotid sinus was shown by Hering in 1923 to play an important rôle in the regulation of the cardiac rate and arterial blood pressure.¹ Compression of the carotid at its bifurcation (so as to raise the pressure within the sinus) caused a marked slowing of the heart rate, vasodilatation and a fall in blood pressure; these effects result though mechanical stimulation of the vagus is carefully avoided. Electrical stimulation of the sinus wall produced similar effects. Pressure upon

¹Sollmann and Brown were the first to describe a depressor reflex of this nature. They sectioned the carotid and obtained a fall in blood pressure when traction was made upon its cephalic end. They showed that the reflex was not affected by section of the vagus but was dependent upon nerve terminals in the wall of the internal carotid.

the common carotid some distance below the sinus (so as to reduce the pressure within the sinus) causes cardiac acceleration, vasoconstriction and a rise in arterial pressure together with, as shown by Heymans, the liberation of adrenaline. The carotid sinus therefore constitutes a mechanism whereby both pressor and depressor effects are mediated. The effects are brought about through the following neural mechanism.

THE SINUS REFLEX ARC. The afferent fibers of the reflex arc are contained in the *sinus nerve*,

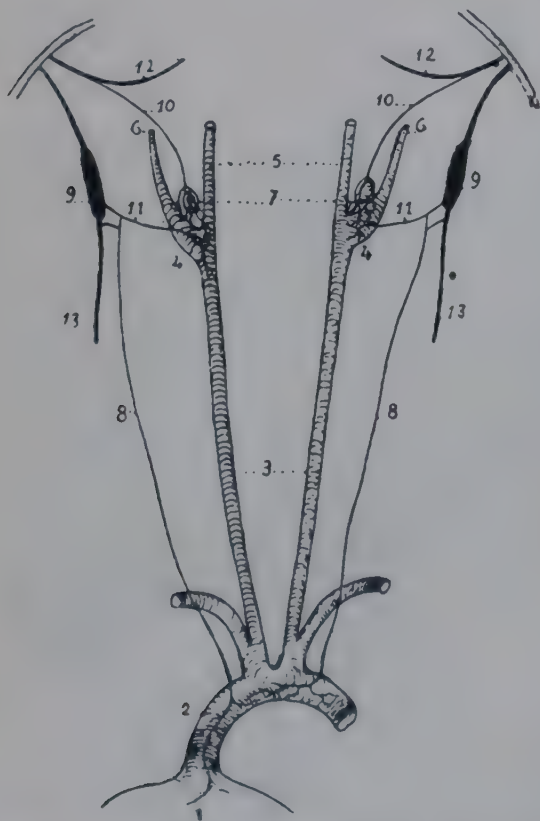


FIG. 106. Innervation of the carotid sinus and arch of aorta. 1, heart; 2, arch of aorta; 3, common carotid; 4, carotid sinus; 5, external carotid; 6, internal carotid; 7, carotid bodies; 8, cardiac depressor nerve; 9, ganglion of vagus; 10, sinus nerve, branch of the glossopharyngeal nerve; 11, nerve branch connecting the carotid sinus with the vagus ganglion; 12, glossopharyngeal nerve; 13, vagus nerve. (After Heymans.)

a branch of the glossopharyngeal. This delicate filament descends between the internal and external carotids to the sinus where its fibers terminate in sensory organs (proprioceptors) situated between the connective tissue fibers in the adventitia of the sinus wall. Fibers also ramify in the carotid body (*glomus caroticum*),² a small

²This structure known also as the *carotid gland* or *intercarotid body* is composed of rounded clumps of polyhedral cells, and possesses a rich network of capillaries of a sinusoid character. Some of the cells stain brown with chromic acid (chromaffin cells, p. 684). The intercarotid body however, does not contain adrenaline, and it is not believed to be an endocrine gland. It is a sensory organ containing chemoreceptors sensitive to changes in the oxygen

structure situated upon a branch of the occipital artery or upon a small vessel arising directly from the external carotid just above the bifurcation of the common carotid. Centrally the fibers of the sinus nerve make connections with the cardio-inhibitory and vasomotor centers. The efferent limb of the cardiac part of the reflex is, of course, the vagus. The efferent limbs of the vasodilator and vasoconstrictor reflexes are apparently sympathetic fibers, for these reflexes are abolished by complete removal of the sympathetic chains. As will be seen from figure 106, a nerve twig connects the sinus with the ganglion of the

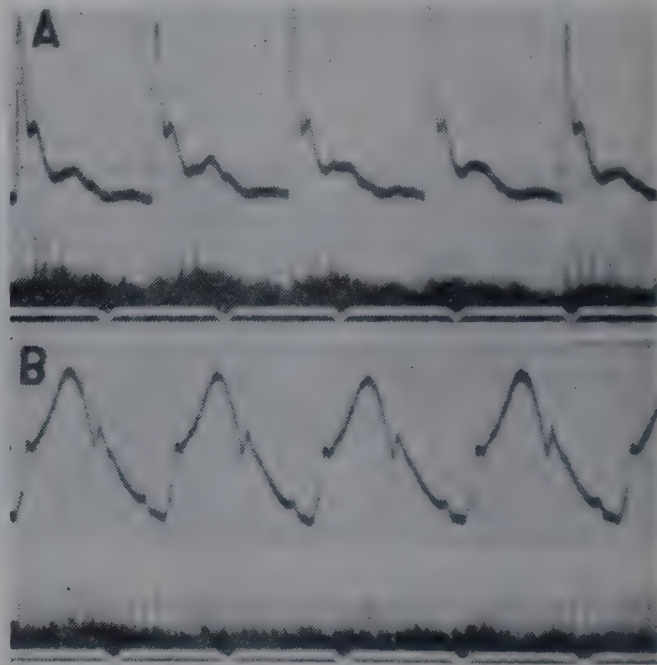


FIG. 107. The upper curve in each record represents the arterial blood pressure registered by a membrane manometer; the lower curve of each record shows the electrical discharge from a single fiber of the carotid sinus nerve of the rabbit. In the upper record (A) the mean arterial pressure was 55 mm. Hg.; even at this low level a discharge of 4 impulses accompanied each ventricular systole. In the lower record (B) the mean arterial pressure was 135 mm. Hg.; in this instance there was a larger and more continuous discharge from the end organ. (Bronk and Stella.)

vagus; it also receives a filament from the superior cervical ganglion of the sympathetic.

The action currents passing along the sinus nerve have been studied by Bronk and Stella and by Partridge. Electrodes were placed upon the nerve and after amplification the potential changes were recorded by means of the oscillograph. At ordinary arterial

tension of the blood and through which reflex changes in respiration are effected (see p. 346). According to Comroe, this body plays little or no part in the control of the circulation. Others, however, (Heymans, Bernthal) claim that through these receptors, as through those in the aortic body, anoxemia or CO₂ excess causes reflex vasoconstriction and a rise in blood pressure.

pressures impulses are discharged throughout the cardiac cycle, their frequency increasing during systole and decreasing during diastole. Following the chief burst of rapid impulses which synchronizes with the main wave of the pulse tracing, a second rise in frequency occurs coincident with the dicrotic wave. A rise in general blood pressure increases the rate of impulse discharge as well as the number of sense organs excited. The latter show slow adaptation (p. 807) so that though the stimulus (distension of the arterial wall) persists the impulse discharge shows little reduction in frequency and when the pressure is very high they extend with little reduction in rate throughout diastole. Bronk and Stella were successful in recording the impulses from a single nerve fiber (fig. 107). The frequency of the impulses rises with increased pressure. At low pressures, impulses are discharged only during systole; but at high pressures they continue throughout diastole. The rate of impulse discharge was found to range according to the height of the arterial pressure from 5 to 140 per second.

The sinus reflexes have been studied exhaustively by Heymans and his associates. They carried out cross-circulation experiments which speak conclusively for the physiological importance of these reflexes in cardiovascular regulation (see fig. 108). The sinus of one dog (B) was isolated from the general circulation and perfused with the blood of another animal (A) in the manner shown in the figure. The nerve supply to the sinus was left intact. When the arterial pressure of dog A was raised, that of dog B, recorded in the femoral artery, fell. Conversely, a reduction in blood pressure of dog A caused a rise in the blood pressure of dog B. In the latter instance, adrenaline liberation also occurred which was a contributory factor in the blood pressure elevation. These effects could not be obtained after denervation of the sinus.

The sinus and aortic nerves, or so-called "buffer" nerves, constitute a mechanism of the utmost importance in controlling the arterial blood pressure and in maintaining the circulation to the brain. The rise in diastolic pressure and the increase in heart rate which occur when the body changes from the recumbent to the sitting position or from the sitting to the standing position, are apparently brought about through these nerves; they therefore play an essential part in compensating for the effect of gravity upon the circulation.

An underfilled state of the vessels, as may result from hemorrhage or shock, or any other condition which tends to cause a fall in blood pressure, will call these mechanisms into play. A general-

ized vasoconstriction results to adjust the vascular capacity to the reduced blood volume and thus maintain the blood pressure. Excessive elevation of the blood pressure, on the other hand, is count-

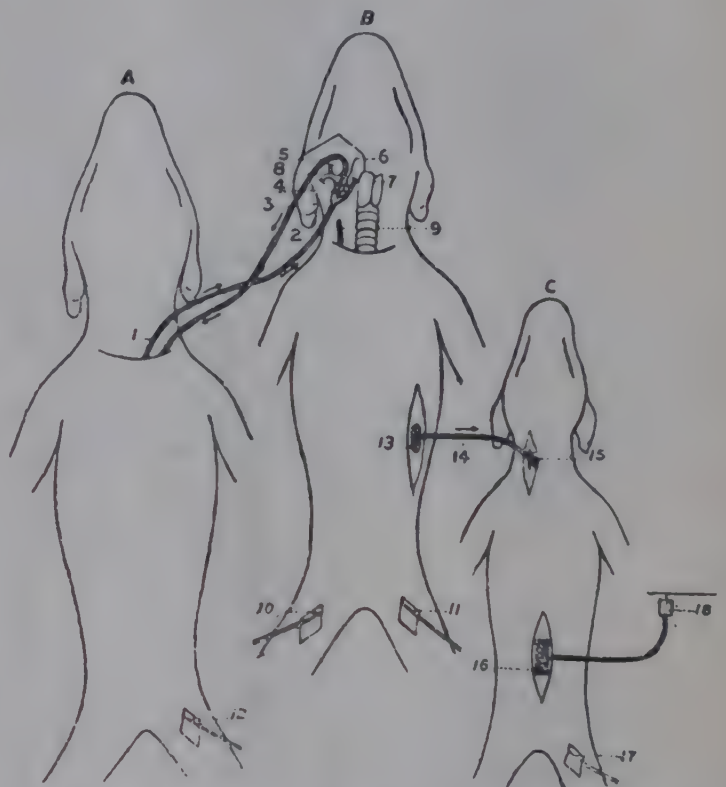


FIG. 108. Scheme of perfusion of the isolated carotid sinus of dog B, by dog A, and an anastomosis between the suprarenal vein of B and the jugular vein of dog C. 1, left carotid artery of dog A; 2, right carotid artery of B, anastomosed with carotid of A; 3, left external jugular vein of A; 4, isolated right carotid sinus of B; 5, lingual artery of B, anastomosed with jugular vein of dog A; 6, nerve supply to carotid sinus of B. The blood from dog A flows through the carotid sinus of dog B and back to A via the lingual artery of B and the external jugular of A. 7, internal carotid; 8, facial and maxillary arteries; 9, common carotid; 10, 11, 12 and 17, femoral arteries to manometers; 13, adrenal gland; 14 and 15, suprarenal-jugular anastomosis; 16, decapsulated spleen in plethysmograph; 18, piston recorder for plethysmograph. (After Heymans.)

ered by a depressor reflex (see diagram fig. 109). The great importance of these reflex mechanisms in hemorrhage is shown by the fact that in an animal in which all four buffer nerves have been sectioned the rapid loss of only about $\frac{1}{10}$ of the blood volume proves fatal, whereas usually a reduction in blood volume of from 35 to 45 per cent is required to cause death. Mayerson found that tilting anaesthetized dogs from the horizontal to the upright position caused a sharp drop in blood pressure followed within 10 seconds by a compensatory rise. After section of both sets of buffer nerves the compensatory rise did not, as a rule, occur.

The cardiovascular effects are brought about through alterations in the frequency of the im-

pulses which are constantly ascending along the aortic and sinus nerves to the cardiac and vasomotor centers. Any increase in the tension exerted upon the proprioceptors in the sinus or aortic wall causes a rise in the frequency of the afferent impulses and, as a consequence, slowing of the heart and vasodilatation. It has been demonstrated by oscillographic methods that during a depressor reflex *efferent* impulses dis-

Several European workers (Hering, Heymans and Bouckaert, and others) have reported the occurrence of permanent hypertension in animals following bilateral section of the sinus aortic nerves. Pressures as high as 200 mm. Hg over a period of three years have been reported. Other investigators who have carried out similar experiments find that the hypertension so produced is not permanent in the majority of animals, but

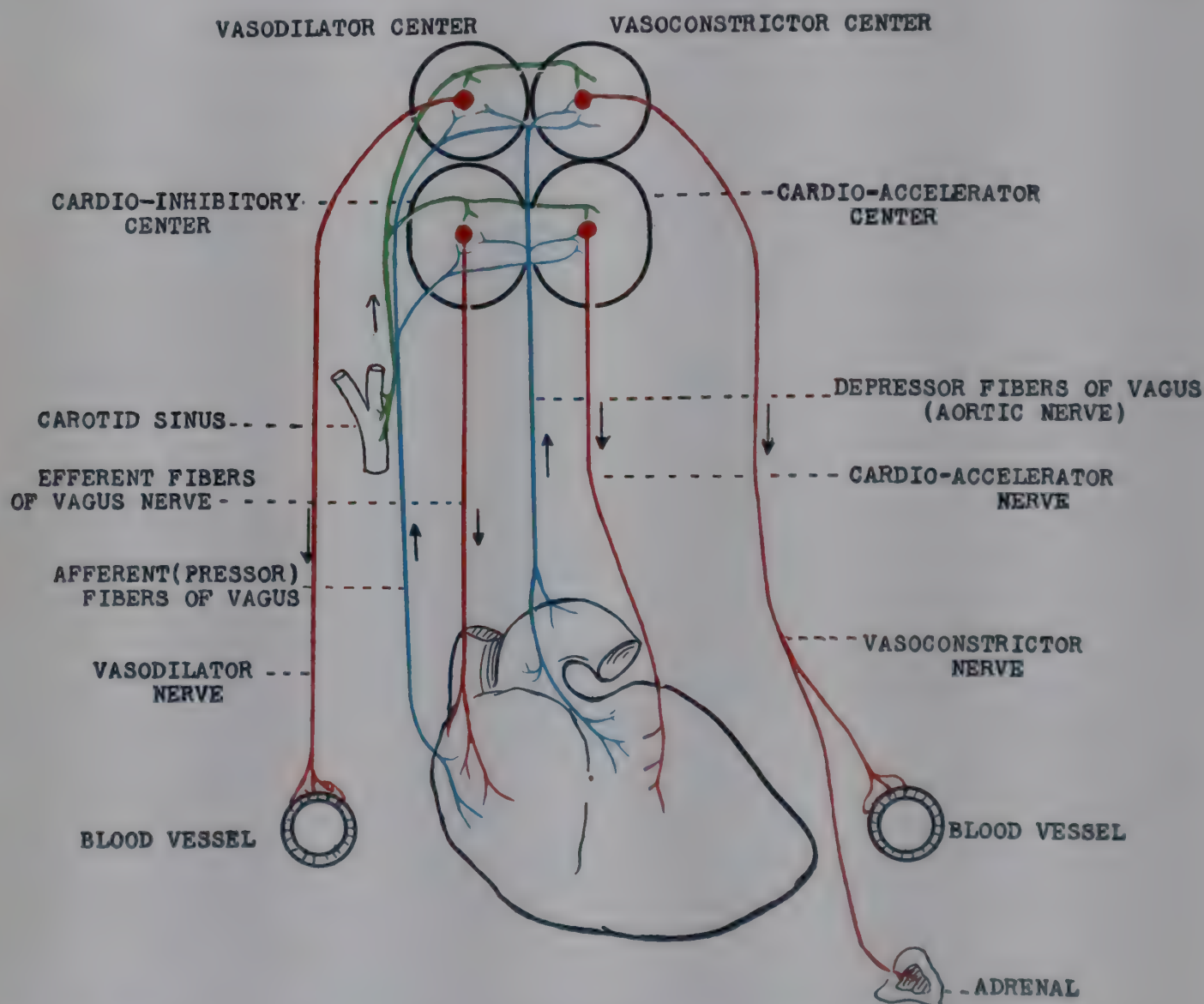


FIG. 109. Diagrammatic representation of cardiovascular reflex mechanisms. Afferent vagal fibers in blue, sinus nerve in green, efferent fibers to the heart and to the blood vessels in red. The afferent fibers are represented as causing reciprocal effects upon the medullary centers (see also p. 245 and fig. 111).

charging over the cardiac accelerator and vasoconstrictor nerves are reduced in frequency or may cease. Reduction in the tension upon the vascular wall, on the other hand, by lessening the intensity of the stimulus to the nerve endings, lowers the frequency of impulse initiation and lessens the tonic depressor effect; a rise in arterial blood pressure results. The rise in blood pressure and increase in heart rate which occur during ether anesthesia, are attributed by Heymans and his associates to depression of the activity of the sinus receptors.

tends to return to normal after a variable period. Such a result may be due to the regeneration of the sectioned nerves or to the reflex control of the circulation being assumed by some other mechanism.

The carotid sinus in man

It is a very old observation that pressure upon the carotid artery in the human subject may cause slowing of the heart (Parry, 1799). Many of the examples in the literature of bradycardia due presumably to pressure upon the vagus were

in all likelihood due to a sinus reflex. Indeed it is very questionable whether the vagus can be stimulated by pressure through the overlying tissues, for in operations upon the neck, even pinching the nerve with forceps does not stimulate it; and in animals, the vagus is relatively unresponsive to mechanical stimulation.

Since the discovery of the carotid sinus, many observations upon the depressor reaction in man have been reported. In paroxysmal tachycardia the rate may often be restored temporarily to normal by the application of pressure to the sinus. Weiss and his associates have shown, however, that the sensitivity of the sinus reflex varies considerably in different individuals. In about 30 per cent of persons with normal cardiovascular systems no response whatever could be obtained. In the remainder the cardiac slowing amounted to less than 6 beats per minute and the fall in blood pressure to less than 10 mm. Hg.

HYPERSENSITIVITY OF THE SINUS (DEPRESSOR) REFLEX. In hypertension and arteriosclerosis the reflex is often unusually sensitive. In from 70 to 78 per cent of cases of hypertension observed by Weiss and Baker, a fall in arterial pressure of from 10 to 105 mm. Hg (average 40 mm.) and a reduction in heart rate of from 4 to 20 beats followed pressure upon the sinus. In a corresponding proportion of arteriosclerotic cases a fall of from 10 to 65 mm. Hg and an average reduction in heart rate of 16 beats per minute resulted.

These observations lend no support to the idea that a failure of the depressor sinus reflex as a result of structural changes in the sinus wall is a factor in the production of essential hypertension. As a matter of fact, marked changes in the walls of the sinus may occur with a normal blood pressure while hypertension may exist though the sinus shows no abnormality.

THE CAROTID SINUS SYNDROME (VASOVAGAL SYNCOPE (LEWIS)). Attacks of dizziness and fainting and sometimes convulsive seizures may result from overactivity of the sinus reflex. An attack may occur without known cause, be induced by emotion or follow slight pressure upon the neck. In one case which has been reported, shaving the skin of the neck overlying the sinus or buttoning a tight collar precipitated an attack. During an attack, marked slowing of the heart and a fall in arterial pressure occur. Extrasystoles, delay in A-V conduction, complete heart block or typical Stokes-Adams attacks may occur. In subjects of these paroxysms hypersensitivity of the sinus mechanism can usually be demonstrated between attacks, slight pressure producing

a pronounced depressor reaction (see fig. 110). In some of these cases no structural abnormality of the sinus is evident, the condition, apparently, being purely functional in nature; in others the sinus shows an aneurysmal dilatation; and in others again, a small tumor in the region of the carotid bifurcation has been responsible. In any event denervation of the sinus relieves the condition. After denervation, the blood pressure rises and the heart rate increases for a few hours but soon returns to normal.

BALANCED AND RECIPROCAL VASCULAR REACTIONS

In the intact animal the height of the blood pressure at any moment, insofar as the nervous control of the peripheral vessels is concerned, is

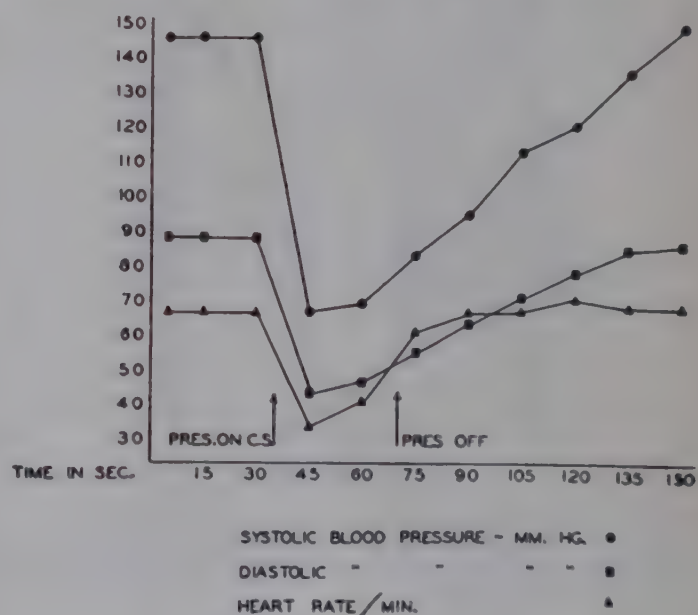


FIG. 110. The effect on blood pressure and heart rate of pressure on the carotid sinus (hypersensitive) in the human subject. Note that both blood pressure and heart rate show a marked fall immediately after stimulation of the sinus. When the pressure is released, the heart rate returns to normal very quickly, the blood pressure more slowly. (After Weiss and Baker.)

apparently the algebraic sum of the effects of afferent impulses impinging upon the vasomotor centers. Under ordinary circumstances impulses arising from the carotid sinus and aortic arch play the most prominent rôle, but impulses from skin, muscles and viscera and from higher nervous centers also exert an important influence. That pronounced effects upon the peripheral vessels can be produced by the irradiation of impulses from higher centers is evidenced by such phenomena as blushing, pallor, erection and certain types of syncope (fainting). The vascular changes observed by Drury and Florey in the mucosa of the exteriorized colon of the dog when the animal was excited; and the changes in splenic volume noted by Hargis and Mann and by Bar-

croft (p. 54) are other examples. Even very mild excitation of psychic centers exerts an influence upon the vascular mechanisms. The psychogalvanic reflex (due to changes in the electrical resistance of the skin) has a vascular basis. A reciprocal relationship also exists between splanchnic and cutaneous vascular areas on the one hand and the vessels of the muscles on the other. Adrenaline, for example, causes dilatation of the latter vessels accompanied by vasoconstriction in the skin and abdominal viscera. Stimulation of the wall of a large vein or distension of the duodenum causes reflex constriction of the cutaneous vessels and stimulation of the skin results in

dilate. Messages pass to the vasomotor center which then discharges vasoconstrictor impulses to the vessels of the area from which the afferent impulses arose. Thus, undue distension of the vessels and pooling of blood in the splanchnic region is prevented. It has also been shown by Izquierdo that stimulation of the peripheral end of the splanchnic nerve causes a much greater rise in blood pressure than usual if the carotid sinuses have been excluded from the circulation (by clamping the carotids). This observation indicates that ordinarily the pressor effect of splanchnic stimulation is largely counteracted by a depressor reflex initiated from the sinus.

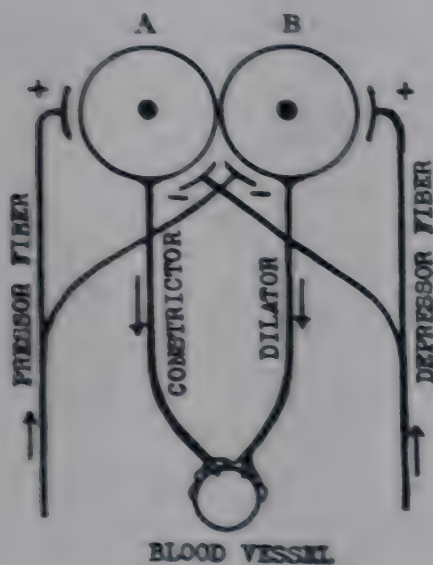


FIG. 111. Illustrating the reciprocal action of the centers in vascular reflexes. A, vasoconstrictor center; B, vasodilator center.

an increase of the blood in the liver and in the renal cortex. Furthermore, the muscular and cutaneous tissues may show opposite vascular reactions. Thus, in the dog, cooling of the body causes constriction of the skin vessels and vasodilatation in the muscles; in man, adrenaline causes constriction of the digital arteries and dilatation of vessels of the muscles.

An interesting example of the complex nature of the reflex vascular adjustments has been described by Bronk and Gammon. An electrical record obtained from a twig coming from a Pacinian corpuscle in the mesentery during perfusion of the mesenteric vessels showed an increase in the frequency of the afferent impulses when the perfusion pressure was raised. The impulse frequency was reduced by bleeding the animal and increased again when the blood was reintroduced into the body. It is suggested that the Pacinian corpuscles which lie in close relation to the vessels are stimulated when the latter

Löwen reflex

This is the term applied to the reaction first described by Löwen, in which a local dilatation of vessels accompanies a general vasoconstriction. When, for example, the central end of an afferent nerve to an organ is stimulated while its efferent vasomotor fibers remain intact, a rise in general blood pressure occurs together with a dilatation of the vessels of the organ. It is evident that in the intact animal such a mechanism, brought into play through afferent impulses arising within the organ itself, will provide it with an increased blood flow during activity.

The reciprocal action of the medullary centers

The experiments of Bayliss and others indicate that the reflex vasomotor effects involve both centers in a reciprocal manner. In the depressor reflex the tone of the vasodilator center is raised while that of the vasoconstrictor center is lowered. Conversely, the vasodilator center is depressed and the vasoconstrictor center excited in a pressor reflex. These reciprocal reactions are shown diagrammatically in figure 111.

It has been generally conceded that in a depressor reflex, loss of constrictor tone is accompanied by increased tone of the vasodilator center. It is also granted, of course, that in a pressor reflex the vasoconstrictor center is stimulated; that depression of vasodilator tone accompanies the constrictor effect but not always been so apparent. The following experiment of Bayliss shows that the latter reaction also occurs. The vessels of the salivary gland were maximally dilated by means of heat and deprived of the constrictors by sectioning the cervical sympathetic. A pressor reflex elicited by stimulating the afferent end of a somatic nerve then resulted in a reduction in blood flow through the gland, which was ascribed to a reduction in vasodilator tone.

VASOMOTOR REACTIONS DURING MUSCULAR EXERCISE

Constriction of the splanchnic vessels occurs at the commencement of muscular exercise. This is attributed to the reception by the medullary centers of impulses discharged from the motor and psychic areas of the cerebral cortex. It is said that splanchnic vasoconstriction actually anticipates the commencement of the muscular effort and may even occur at the thought of taking exercise, though no actual movement is made. If the muscular effort is very strenuous, a rise in hydrogen ion concentration may occur and act as a stimulus to the vasomotor center. In ordinary exercise, however, no appreciable change in reaction of the blood as a whole occurs and even in the more severe types of muscular exertion a change in blood reaction is of minor importance in the production of the splanchnic vasoconstriction. The small vessels of the muscles dilate during exercise but this, as described on page 249, is a direct action upon the vessels of substances produced in the muscles themselves; though it is possible that the nervous centers do play a part in this reaction there is no evidence for this. The arterial blood pressure is highest in the earlier periods of the exercise when the systolic level may reach a height of 180 mm. Hg or more. Vascular readjustments, e.g., cutaneous vasodilatation and possibly a reduction in the degree of splanchnic vasoconstriction, tend to occur as the exercise continues; some reduction in the blood pressure results. Within 10 seconds or so after the cessation of the exercise, the pressure falls to normal but rises abruptly again to its previous level, then gradually declines and finally reaches the normal value in from one to four and a half minutes. These fluctuations in the arterial blood pressure following the exercise are not, however, of nervous origin but are due to mechanical factors (see p. 127).

An interesting reflex mechanism in the hypertension of exercise has been demonstrated in the human subject by Alam and Smirk. Contractions of even a small group of muscles, e.g., those moving the little finger, while the circulation through the arm was arrested, caused a rise of as much as 70 mm. Hg. Cerebral influences cannot be mainly responsible for the rise since it persisted, provided that the arm circulation was occluded, for some time after the exercise had ceased. Any effect of muscle metabolites upon the nervous centers is, of course, excluded since none could enter the general circulation. For the same reason increased

venous return to the heart cannot be a factor in the pressor effect. Arrest of the circulation alone was ineffective. The phenomenon, like the reflex acceleration of the heart (p. 210), is apparently due to the stimulation of afferent endings in the muscles by metabolites accumulated as a result of the circulatory arrest. Of how much importance such a reflex is in ordinary exercise, i.e., with free circulation through the muscles, it is difficult to say.

The effects of exercise upon other physiological functions are dealt with in other sections of this book. The reader is referred to the index under Muscular exercise.

AXON REFLEXES

These are not true reflexes, since no nerve cell is involved. The efferent and afferent limbs of the axon reflex arc are formed by the branching

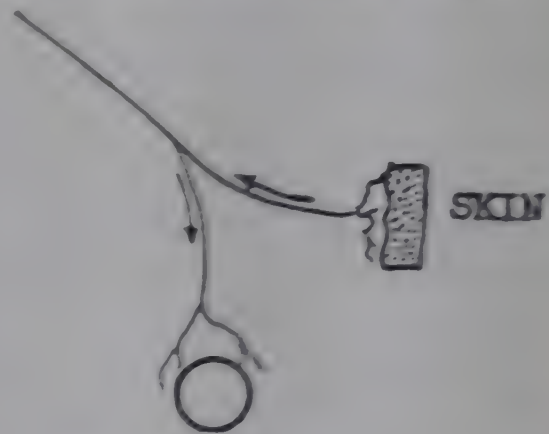


FIG. 112. Axon reflex. Description in text.

of a single nerve fiber. A stimulus applied to one branch sets up an impulse which travels centrally to the point of division from where it is reflected down the other branch to an effector organ. The most familiar type of axon reflex is that which involves a sensory nerve fiber and through which vasodilator effects are brought about. Ninian Bruce has made a study of the superficial vasodilatation which results from cutaneous or conjunctival stimulation, and offers convincing evidence for the dependence of these reactions upon axon reflexes. Spiess had remarked some years before that in inflammatory states of the superficial tissues the more painful the part became, the greater was the development of heat and redness. The degree of dilatation of the vessels seemed to be dependent upon and directly proportional to the pain experienced. A local anesthetic reduced the pain and the inflammatory reaction as well. Bruce found that the dilatation of the vessels which results from the application of an irritant, such as mustard oil,

to the conjunctiva of an animal can be prevented if the sensory nerve endings are first paralyzed by means of cocaine (or better, alypin, which has no direct effect upon the vessels). On the other hand, if the mustard oil be applied shortly after division of the fifth nerve, which also renders the conjunctiva insensitive, the usual inflammatory reaction occurs. Yet if sufficient time be allowed to elapse after division of the nerve for degeneration of the sectioned sensory fibers to take place, the conjunctival reaction to irritants cannot be elicited. Corresponding results were obtained in experiments upon the skin of the trunk. The employment of a local anesthetic abolished the reaction. It was obtainable after section of the posterior roots peripheral to their ganglia, so long as degeneration of the sensory fibers had not occurred, but was abolished after this. The vasodilator reactions cannot, therefore, be due to a central reflex, yet they are dependent upon the integrity of the sensory nerve fibers. Since no peripheral nerve cells are known to exist through which such a reaction could occur, the latter must, it is concluded, be due to an axon reflex. The impulse evidently passes up a sensory fiber and then down (i.e., antidromically) a collateral branch supplying an arteriole (fig. 112). See also page 268. Knowledge of these local reactions has obviously wide applicability to the investigation of lesions of the superficial tissues associated with vascular changes, and especially those of an inflammatory nature. They afford another example of the close association between the transmission of pain and vasodilator effects (p. 235).

It may be mentioned incidentally that axon reflexes are not confined to afferent fibers and to vasodilator reactions. The discovery of axon reflexes was made by Langley and Anderson in the investigation of an observation of Sokolowin's, namely, that when the central end of the hypogastric nerve of one side was stimulated, contraction of the opposite half of the bladder occurred. The impulse was shown to have passed centrally for a short distance to an axon branch along which it was transmitted to the inferior mesenteric ganglion of the opposite side from where it was relayed to the vesical muscle. Axon reflexes were later shown by these observers to occur in other parts of the autonomic nervous system (through the ganglia of which no true reflexes occur). The preganglionic fibers of a given spinal segment do not necessarily terminate in the first ganglion of the lateral chain which they enter but pass along the chain for some distance giving off collaterals (axon branches) to cells in the ganglia through which they pass, or they may make no connections until they have

reached a level several segments below that of the segment from which they originated. Therefore, when the sympathetic cord was cut and its central end stimulated, pilomotor and vascular effects were produced in skin areas lying at a higher segmental level than the point of stimulation. That axon reflexes of a more local nature occur in the autonomic plexuses of the intestine and other hollow viscera is generally conceded.

THE BLOOD GASES, LACTIC ACID AND HISTAMINE IN THEIR RELATION TO THE VASCULAR MECHANISMS

CARBON DIOXIDE EXCESS AND OXYGEN LACK. ASPHYXIA

The vasomotor centers are highly sensitive to the gaseous composition of the blood flowing through their vessels.

A high carbon dioxide tension or a low oxygen tension causes an increase in vasoconstrictor tone and a rise in blood pressure. The persistent elevation of the blood pressure which results from a rise in *intracranial pressure* (e.g., cerebral tumor or hemorrhage) is due to compression of the medullary vessels and the interference with the blood supply to the centers; and the marked pressor effect induced by *asphyxia* is the result of the excitation of the vasoconstrictor center by the more venous character of the blood. Three stages in the circulatory effects of asphyxia can be distinguished: (1) For a time after the respiratory muscles of an animal have been paralyzed by curare little change in the level of the blood pressure occurs. (2) In a minute or two the blood pressure, as a result of the arteriolar constriction, commences to mount and may soon reach a value more than double the normal. The vasoconstriction is undoubtedly enhanced by adrenaline liberation, the hormone exerting a direct action upon the vessels. The heart at this time, as a result of the fuller relaxation of the cardiac muscle and the increased venous inflow, beats forcibly; the rate is slowed in consequence of the rise in blood pressure as well as by the action of carbon dioxide upon the cardio-inhibitory center and the tissue of the sino-auricular node. The effect of the carbon dioxide excess upon auriculo-ventricular conduction may result in heart block (p. 190). The capillaries and small veins are dilated and intense cyanosis (p. 375) occurs. (3) The blood pressure falls. This is due to failure of the heart as a result of the anoxemia, and not to the release of the arterioles from the constrictor influence, for, if the volume of the

dney be recorded at this time it will be found that no change occurs before death.

The hypertonicity of the vasoconstrictor center in asphyxia might be due either to the carbon dioxide excess or to oxygen lack. Mathison, however, has studied these two influences separately. When an animal breathed an air mixture containing 10 per cent of carbon dioxide with an equate percentage of oxygen, the arterial blood pressure changed almost immediately, rising within less than a minute to double its previous height; the intestinal volume fell (fig. 113, a). Oxygen lack alone, produced by the inhalation of nitrogen, caused a pressure rise of about the same magnitude; the response was delayed for half a minute or so but was then abrupt (fig. 113, b). Injections of lactic acid or other organic acids into the blood stream produced effects which were in general similar to those of carbon dioxide excess or oxygen deficiency (fig. 113, c). These three factors, carbon dioxide excess, oxygen lack and a rise in hydrogen ion concentration by the injection of lactic acid act upon the vasomotor center and the chemoreceptors of the carotid and aortic areas in a manner analogous to that described for respiratory control (p. 346). Thus, the action of O_2 is exerted mainly upon the center, whereas hypoxemia (or cyanide which suppresses oxidative processes) and acid injections act in a common fashion by raising the H ion concentration of the chemoreceptors.

The spinal centers are also sensitive, though to a less degree, to a rise in hydrogen ion concentration. In the decapitate animal, for instance, under artificial respiration, a rise in blood pressure does not occur until the carbon dioxide percentage of the inspired air has reached 20 per cent, whereas breathing a 5 per cent carbon dioxide mixture may be sufficient to excite the medullary center.

The local effect of carbon dioxide excess or of lactic acid upon the peripheral vessels is one of dilatation. The central and peripheral effects of the hydrogen ion are therefore opposite in direction. During exercise, for example, the acid metabolites formed in the active muscles cause dilatation of their small vessels. On the other hand, any rise in the hydrogen ion concentration of the blood as a whole which may result will, through an action upon the medullary center, cause splanchnic vasoconstriction. Such an effect will contribute to the general rise in blood pressure accompanying exercise (p. 247). The rise in arterial pressure, combined with dilatation

of the vessels within the muscles themselves leads, of course, to a maximum blood flow through the active tissues. It has already been mentioned, however, that unless the exercise is very strenuous no change in blood reaction occurs; and in any event it appears that, as compared with purely

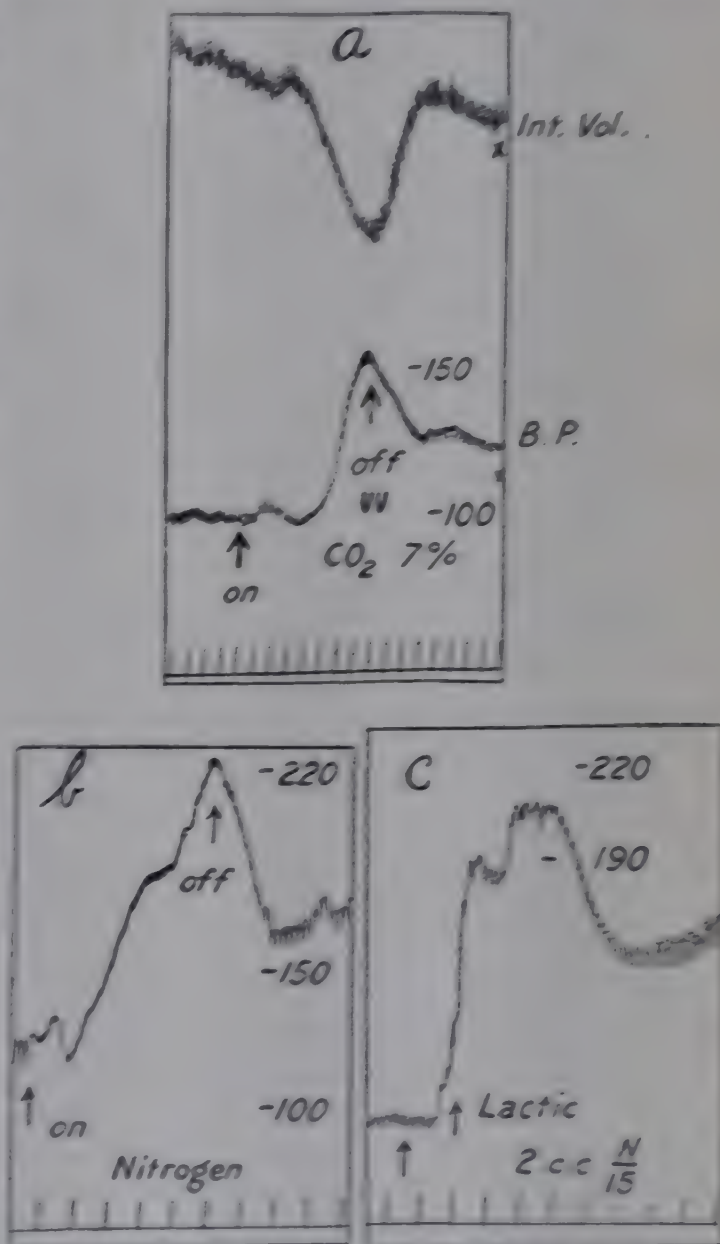


FIG. 113. Showing the pressure effect of carbon dioxide excess, oxygen lack and lactic acid injections. a, tracings of intestinal volume (upper curve) and of blood pressure in an experiment in which a mixture containing 7 per cent CO_2 was breathed. b, shows the rise in blood pressure during the breathing of nitrogen, and c, the rise in arterial pressure resulting from the injection of lactic acid. (After Matheson.)

nervous mechanisms (e.g., irradiation of impulses from cerebral centers), the effect upon the vasomotor center of an increase in hydrogen ion concentration plays a minor rôle in the hypertension of muscular effort. The local vasodilator effect of the hydrogen ion, on the contrary, is of the utmost importance.

The work of Anrep and his associates indicates

that histamine liberation is also a factor in the local vasodilator reaction. These observers found that, whereas the histamine concentration in the venous blood coming from a resting muscle was the same as that in the arterial blood, during contraction of the muscle, the histamine concentration in the venous blood exceeded that of the arterial blood.

CARBON DIOXIDE DEFICIT

Carbon dioxide depletion (acapnia) produces effects upon the vascular system which, in general, are the reverse of those resulting from carbon dioxide excess. The tone of the constrictor center is lowered; arteriolar dilatation results and the blood pressure falls. The *direct* effect of the carbon dioxide lack upon the peripheral vessels is to increase their tone. The capillaries and venules are apparently more responsive to the local action than are the arterioles upon which the central effect predominates.

The effects of carbon dioxide deficit upon the circulation have been studied by Dale and Evans. They found that when cats were over-ventilated at the rate of from 100 to 180 respirations per minute there occurred a rapid and profound fall in blood pressure (to 30 or 40 mm. Hg within a minute or two). In these experiments the depressor effect was due chiefly to the loss of arteriolar tone; the effect of the loss of carbon dioxide or of the respiratory movements (p. 213) upon the action of the heart played an unimportant part. When the excessive ventilation was carried out, using an air mixture containing 5 per cent carbon dioxide, the fall in pressure did not occur, or was observed only at the beginning of the period of hyperventilation. The depressor effects of acapnia were also obtained in decapitated animals, thus indicating that the spinal vasomotor centers are also highly sensitive to carbon dioxide deficit. After destruction of the cord, changes in the tension of the gas caused reverse effects, namely, a rise in pressure with carbon dioxide deficit and a fall with carbon dioxide excess; the direct actions upon the vessels (constriction and dilatation respectively) being then unopposed by the central influence.

In the human subject the effect of forced breathing upon the blood pressure varies. In the majority a fall in pressure results but in some the pressure remains unchanged; in a few it rises. The depressor effect when it occurs is not due altogether to the effect of carbon dioxide deficit upon the vasomotor center but is largely

the result of the mechanical effect of the forcible expiratory movements (p. 213) which impede the venous return to the heart (Vincent and Thompson). This is evidenced by the fact that in many persons the depressor effect can still be produced when the forced breathing is carried out with air containing a high percentage of carbon dioxide. In those persons in whom the pressure does not fall, its failure to do so may be due to the irradiation of impulses from the motor area to the vasomotor center which enhances the latter's tone, or to the compensatory vasoconstriction resulting from the local effect of the carbon dioxide deficit. Vasoconstriction of the cutaneous vessels is often clearly evident from the pallor which occurs in the period of apnea following forced breathing; the cutaneous circulation is sometimes slowed to such a degree that cyanosis appears. Stewart by means of his calorimetric method, has also demonstrated under such circumstances the slowing of the blood flow through the hands. Furthermore, if the vessels are kept maximally dilated by means of a hot bath, in a subject who ordinarily either shows no blood pressure effect as a result of forced breathing or gives a pressor response, then acapnia causes a depressor effect. The antagonism between the central and local effects of carbon dioxide upon the vessels can also be demonstrated by applying a tourniquet to the arm. Forced breathing then causes a much less marked effect upon the vessels of the asphyxiated arm (owing to the high carbon dioxide tension in the blood of the obstructed vessels) than upon those of the opposite arm.

Traube-Hering waves

These are slow, rhythmical waves which appear on the blood pressure tracing of an animal poisoned by curare, absinthe, morphine and certain other drugs. They also appear in asphyxia or in any condition in which the oxygen in the blood supplying the medulla is markedly reduced or the carbon dioxide content increased. They may therefore appear in hemorrhage or when (as a result of raised intracranial pressure) the circulation through the medulla is interfered with. The frequency of the waves is from 5 to 10 per minute. They are due, apparently, to periodic variations in tone of the vasomotor center and should not be confused with those of splenic origin (p. 54).

THE CONTROL OF THE VEINS

The veins receive constrictor fibers from the sympathetic. The innervation is not confined to the minute veins, but includes the larger superficial veins of the limbs, intestines, spleen, liver and kidney. There is no evidence, however, that the venae cavae or the veins of the muscles are furnished with constrictor nerves. Like the arteries, veins exhibit constrictor tone, dilating when their nerves are sectioned. The vein wall responds readily by constriction to direct mechan-

cal stimulation, e.g., puncture by a needle. Certain superficial veins receive dilator impulses (antidromic) via sensory fibers. Dilatation of the inferior mesenteric vein has also been observed following stimulation of the posterior nerve roots of the lower thoracic segments. In emotional states constriction of the superficial veins has been observed and reflex changes in caliber, analogous to those occurring in the arterioles, result from various types of peripheral stimulation. According to Heymans the veins take part in the pressor or depressor reflex induced from the carotid sinus.

Carbon dioxide acting locally upon the venous walls exerts a dilator effect; reduction in carbon dioxide tension increases venous tone. Yandell Henderson and associates attach a great deal of importance to the tonic influence exerted upon the venous mechanism by carbon dioxide. They claim that acapnia produces constriction of the peripheral veins and so interferes with the return of blood to the heart (p. 213). The rise in venous pressure which results from breathing an air mixture rich in carbon dioxide they ascribe to relaxation of the smaller veins and the increased flow of blood from the arterial side.

The reactions of the veins to adrenaline, pituitrin and several drugs are similar to those of the arterioles to such agents.

MEANS EMPLOYED TO DEMONSTRATE THE PRESENCE OF VASOCONSTRICTOR OR VASODILATOR FIBERS IN A PERIPHERAL NERVE TRUNK

If both types of vasomotor fibers exist in a given nerve the constrictor effects predominate when the nerve trunk is stimulated and may obscure entirely any coincident excitation of dilator fibers that may occur. In order, therefore, to demonstrate the presence of the latter it is necessary to remove the constrictor influence before stimulating the mixed nerve. This may be accomplished by sectioning the nerve and allowing time for *degeneration of the vasoconstrictors* to occur, which is some time (2 to 3 days) in advance of the degeneration of the dilators. At the end of this time, therefore, pure vasodilator effects are obtained. The two types of fibers also respond more readily to *different kinds of stimuli*, and this fact may sometimes be employed to detect the presence of vasodilator. The vasoconstrictors respond more readily to strong electric shocks of high frequency, the dilators to comparatively weak and slow rhythmic shocks. The

latter also respond more readily to mechanical stimulation. *Ergotoxine* is a drug which acts in a selective manner, as shown by Dale, by abolishing motor effects of the sympathetic nervous system. The vasoconstrictors are paralyzed but the vasodilators are unaffected. Therefore when a nerve, such as the splanchnic, which contains both types of fibers is stimulated after administration of this drug, the response is one of pure vasodilatation.

Several methods are available for the demonstration of the actual vasoconstrictor or vasodilator effect. (1) *Inspection* of the organ or vascular region supplied by the nerve under investigation. Flushing or blanching indicates vasodilatation or vasoconstriction respectively. The method is particularly suitable to superficial and transparent structures, such as the frog's web or the ear of the rabbit; the latter was employed by Claude Bernard when he discovered the vasomotor nerves.

(2) *Change in temperature* of a superficial part supplied by the stimulated nerve. The blood in the deeper tissues is considerably warmer than that flowing through superficial vessels. When the arterioles dilate the part becomes flushed with blood drawn from deeper regions, i.e., the cutaneous blood flow is increased; the temperature rises in consequence. A reverse effect upon the superficial temperature is caused by vasoconstriction. The temperature changes may be detected by means of a sensitive thermometer held in contact with the surface or, more precisely, by a thermo-electric couple inserted into the tissue, e.g., the skin, mucous membrane, etc.

(3) *Plethysmographic method*. The principles of this method have been explained elsewhere (p. 149). It is applicable to the demonstration of vascular changes in such organs as the kidney, the intestine or a limb, which can be isolated from surrounding parts. The instrument registers changes in volume and these, when they follow stimulation of the nerve supplying the region, are taken to indicate corresponding changes in the caliber of the vessels. Both artery and vein leading to and from the organ must be equally free from compression, since interference with the flow through one or other vessel will cause alterations in volume of the part. When a limb is under investigation it is usually desirable to eliminate muscular movement by the administration of curare. It is essential that changes in volume resulting from passive distensions or collapse of the vessels by changes in the general

arterial blood pressure be distinguished from active vasodilatation and vasoconstriction, respectively. That is, a rise in the arterial blood pressure may cause greater filling of the vessels in a purely passive manner and swelling of the organ in consequence—a mere distension of the vascular

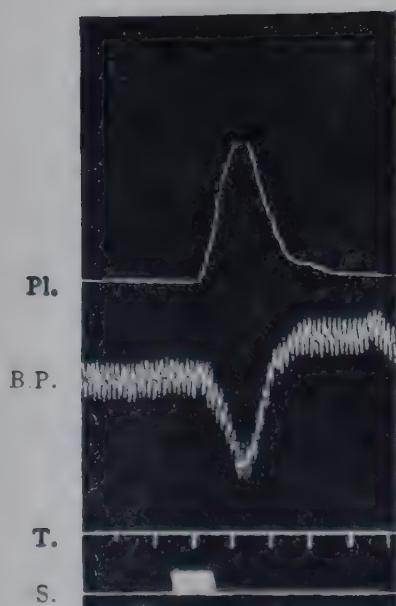
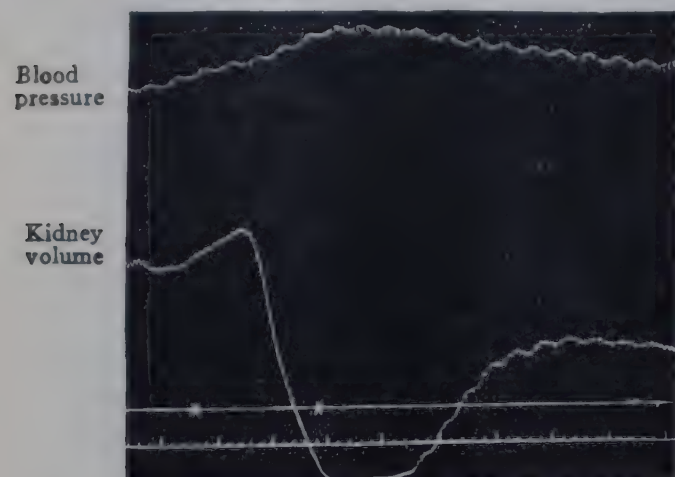


FIG. 114. Upper figure shows simultaneous tracings of carotid blood pressure and volume of kidney. Between X and X the peripheral end of the divided tenth dorsal nerve was stimulated. Time-marking = seconds. (After Bradford.) Lower figure shows the effect upon the kidney volume (Pl.) and arterial pressure (B.P.) of stimulating the central end of the vagus T, time-marker; S. stimulus. (After Bayliss.)

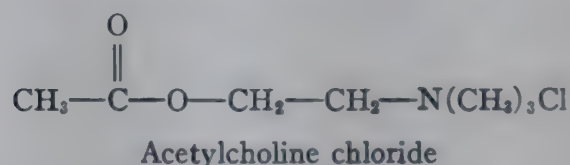
bed. On the other hand, a fall in general blood pressure may drain blood from the organ and cause its volume to shrink. For these reasons a blood pressure tracing must always accompany the plethysmographic records. Only when the blood pressure tracing remains unchanged or the two tracings take opposite directions, i.e., a rise in arterial pressure accompanied by a fall in volume or a fall in pressure coinciding with a rise in volume, can a definite conclusion regarding the change in the caliber of the vessels be drawn (fig. 114)

(4) *Outflow from veins.* In a small organ, such as the salivary gland, changes in the blood flow through it may be detected by noting the rate of flow and color of the blood issuing from the veins. Usually the smaller veins are tied off and the blood as it issues from one or two larger veins collected in a graduated receptacle.

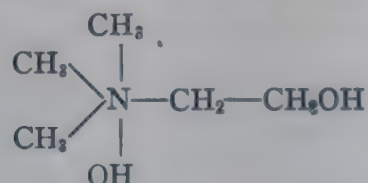
The *thermo-stromuhr* (p. 145 and p. 277) may also be employed to determine variations in the volume flow through the organ, the measurement being made either of the ingoing or outgoing blood.

Vasodilator substances. The results of experimental work in the last few years have added several new names to the list of vasodilator substances which may be extracted from the tissues.

Acetylcholine. More is known about the physiological significance of this choline ester than of any of the other vasodilator substances. Its formula is:

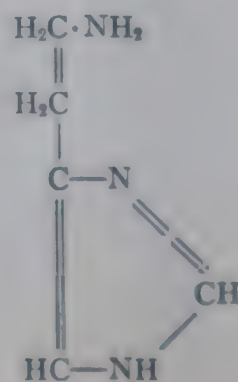


Acetylcholine, as discussed elsewhere (p. 946), is liberated from parasympathetic postganglionic nerve endings and from the preganglionic endings of both parasympathetic and thoracic autonomic fibers. *Choline* itself, which has the following formula



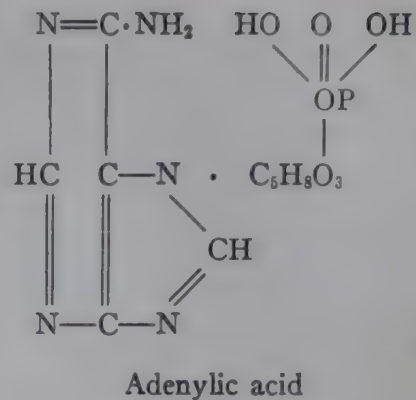
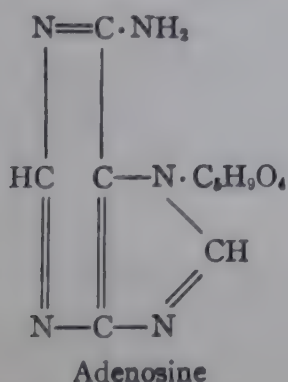
and as a constituent of lecithin and sphingomyelin (p. 595), has an extremely wide distribution in the body, is a well-known vasodilator. Its activity is of a low order in comparison with acetylcholine, the vasodilator effect of choline being increased by at least one thousand times after acetylation. There appears to be very little free choline in the body, and the amount of acetylcholine, rather than choline, appears to vary under physiological conditions. Choline acts in the same manner as acetylcholine on the blood vessels. Its action on liver fat has been discussed elsewhere (p. 602).

Histamine:



Histamine is also very widely distributed in the body. It can be readily formed *in vitro* by the action of bacteria of the colon typhoid group upon the amino-acid histidine. This mechanism probably accounts for the formation of histamine in the intestine. The method by which histamine is formed in tissues has not been established. Small amounts are present in muscle, while the lung in herbivora and the liver and intestinal tract in omnivora may contain relatively large amounts. The concentration of histamine in human blood is from 1 to 8 micrograms per 100 cc. This is contained mainly in the white cells and most probably in the eosinophils (Code). A substance indistinguishable from histamine is apparently responsible for the first part of the triple response in skin (p. 268) but chemical identification has not been made. "Gastrin" and histamine (p. 434) are indistinguishable. The subcutaneous injection of one-quarter to one-half milligram of histamine produces a copious flow of acid gastric juice in man (p. 442). The mechanism of action of histamine on the blood vessels varies with the species studied, but in man both arterioles and capillaries are dilated. The intravenous administration of a ten-thousandth of a milligram causes an appreciable fall of blood pressure in the etherized cat. One-thousandth of a milligram given intravenously produces a sharp fall of blood pressure in unanesthetized man. The unanesthetized organism is not so susceptible to histamine as the anesthetized. While Abel's researches indicated the wide distribution of histamine in biological material the base was first prepared in crystalline form from perfectly fresh tissue by Best, Dale, Dudley and Thorpe. The possibility that histamine may possess physiological significance has been materially increased by the finding that it is liberated in anaphylactic shock from the liver in the case of the dog and from the lung in the guinea-pig. Histamine may not be the only substance liberated in this condition but it accounts for most of the signs of anaphylaxis. It is important also, as Kalk has shown, that irritation of the skin in certain susceptible people (dermographism) produces a definite secretion of acid gastric juice quite comparable to that which the subcutaneous injection of histamine might evoke. Histamine is destroyed by an enzyme system, histaminase (Best and McHenry) which is found in various tissues, but particularly the kidney and small intestine. The physiological significance of this enzyme has not been established.

Adenosine and derivatives:



In 1929 Drury and Szent-Györgyi showed that the active constituent of certain extracts from skeletal and cardiac muscle which produced a characteristic condition of heart block in the guinea-pig was adenosine. This substance was also shown to have a peripheral vasodilator effect, which has been found to be exerted mainly, if not entirely, upon the arterioles. The heart block (p. 190) produced by adenosine is relieved by barium. Adenosine administered subcutaneously causes a migration of leucocytes to the site of injection, an effect which is not produced by histamine. Histamine and adenosine may both be concerned in inflammatory reactions and in the effects upon the circulation produced by extensive tissue damage. Their exact significance in this connection awaits further investigation. Adenosine and adenylic acid are relatively inert vasodilators with a potency of somewhat the same order as choline. They may be present, however, in considerable amounts in certain tissues.

Kallikrein. Kallikrein is the name given by Frey and Kraut to a vasodilator substance obtained from normal urine. This substance has not yet been obtained in pure form, but it probably differs from all other vasodilators. It does not cause constriction of the bronchioles in the guinea-pig, as histamine does; it lowers the blood pressure of the rabbit, while histamine does not do so when the ordinary anesthetics are used. This substance is rapidly destroyed by blood serum, but the activity is recovered when acid is added. It is suggested that kallikrein is liberated when the tissues become acid through metabolic activity. This would, of course, produce vasodilatation and increased blood flow. The site of formation of kallikrein is not known, although pancreatic tissue has been used for its preparation.

Identification of vasodilator substances. In addition to these substances there are undoubtedly others which cannot be exactly characterized as yet. The vasodilators we have mentioned may be identified by the following means. Kallikrein and adenosine and its derivatives are destroyed by acid hydrolysis; choline and histamine are resistant to this procedure. Acetylcholine is very susceptible to alkali and may be completely destroyed in a short time in a solution at pH 8 to 9. Atropine antagonizes the action of choline or of acetylcholine but exerts no effect upon the action of histamine. Positive evidence for the presence of

adenosine is its characteristic effect upon the guinea-pig's heart. Kallikrein will produce a fall in blood pressure in the atropinized rabbit, which neither choline nor acetylcholine will do, while it exerts no effect on the guinea-pig's heart. These vasodilators may also be separated by the use of precipitating agents and by other chemical procedures.

VASOCONSTRICTOR SUBSTANCES. Among the best known vasoconstrictor agents are *pituiridin* and *adrenaline* (p. 686) and compounds chemically related to the latter, e.g., *ephedrine*, *tyramine* and *benzedrine*. *Barium chloride* is also a powerful vasoconstrictor. *Tobacco smoking* is generally stated to cause peripheral vasoconstriction, the effect being usually not demonstrable unless the smoke is inhaled. The experiments of Bolton, and associates and of Mulinos and Shulman throw doubt upon the conclusion that the vascular effect is due to the absorption of some constituent of the inhaled smoke. They found that a deep inspiration of pure air causes a marked reflex constriction of the cutaneous vessels of the forearm and hand. The phenomenon is enhanced by an irritant or painful stimulus, e.g., inhalation of smelling salts, pinching the skin, etc., and is more pronounced if the respiratory movement is mainly thoracic. Helmer and his associates have shown that the vasoconstrictor agent found in the urine of smokers is nicotine, which they have isolated in crystalline form as a picrate. *Sodium nitrite* contrary to the general belief, causes, as shown by Weiss and his associates, arteriolar constriction. The fall in blood pressure which follows the administration of an appropriate dose, and which may result in collapse and syncope when the subject stands is due to the reduction in venous tone and, as a consequence, the pooling of blood in peripheral veins. The effects produced by nitrite, namely, the fall in blood pressure, slowed peripheral blood flow, acceleration of the heart and fall in venous pressure, are identical, according to Weiss with the peripheral circulatory collapse seen clinically (e.g. in pneumonia and other infection, and in surgical shock).

PERIPHERAL VASCULAR DISEASE

RAYNAUD'S DISEASE

In this condition, which was first described by Raynaud in 1862, the fingers, sometimes the toes or rarely the ears and nose, are the seat of periodic attacks of vascular spasm. The attack lasts as a rule for a few minutes, but may persist for an hour or two. The spasm is usually induced by exposure to cold and frequently appears in symmetrical parts on the two sides of the body. The affected members become cyanosed and cold, later intensely pale and numb (dead fingers). The color change commences in the finger tips and spreads toward the bases of the fingers. As the attack passes off the part again becomes cyanotic, then red and hot; the numbness is re-

placed by burning pain. According to Lewis the spasm involves the digital arteries. The pulse at the wrist or ankle persists during the attack. The local asphyxia may lead to ulcers, scleroderma, rarefaction of the terminal phalanges, and other trophic changes. Gangrene, it is said, sometimes results; it is likely, however, that when this occurs the vascular condition should not have been classed as a true example of Raynaud's disease, but that the vessels had been the seat of structural changes which obliterated their lumina rather than of a simple spasm.

The disease, since Raynaud's first description of it, has been generally attributed to hyperactivity of the vasomotor (vasoconstrictor) nerves. Sympathetic ganglionectomy is, therefore, frequently resorted to in an effort to abolish the attacks. Lewis has shown, however, that a typical attack may be induced in a subject upon whom this operation has been performed, by exposing the affected part to cold (as by immersing it in cold water). He concludes therefore that the fault lies not in the nervous control but in the vascular wall itself. The following observations cited by Lewis substantiate his view.

(1) If one finger of a subject of the disease be immersed in cold water, an attack confined to this finger may be induced. Such a localized result cannot be explained upon the basis of a nervous reflex.

(2) Anesthetization of the ulnar nerve of a normal person by means of novocaine causes dilatation of the vessels of the little finger (removal of vasoconstrictor tone). The vascular spasm in Raynaud's disease cannot be released in this way.

(3) If a subject suffering from Raynaud's disease affecting both hands, and upon whom a unilateral ganglionectomy had been performed, be seated in a cool room with both hands placed in cold water, the vascular spasm which results is more pronounced on the non-sympathectomized side. If, however, the rest of the body is warmed while the hands are immersed in cold water, the attack is more pronounced on the sympathectomized side. In the first experiment the greater degree of spasm on the non-operated side is attributed to the added effect of a vasoconstrictor reflex. The greater degree of spasm on the operated side in the second experiment is attributed to the absence of dilator sympathetic fibers. Though a nervous influence is evident in these observations the essentially local nature of the fault is also indicated.

Ganglionectomy, even though it does not remove the fundamental cause of the condition, does, nevertheless, exert a decidedly beneficial effect. The attacks are less frequent and intense after the operation; normal vasoconstrictor tone and,

as just indicated, the reflex responses to cold having been abolished, a more intense reaction of the arterial wall itself must occur before arrest of the circulation to the part can result.

Simpson, Brown and Adson on the other hand, do not consider that Raynaud's disease is due primarily to a fault of the vascular tissue. These observers maintain that only in the advanced stages of the disease is the vascular wall itself abnormal and that in milder cases the fault is essentially vasomotor in character. They point out that Lewis' crucial experiments were performed upon severe or complicated cases of the disease.

ERYTHROMELALGIA

Erythromelalgia is a rare but interesting condition characterized by attacks of painful redness of one or both feet, or occasionally of the hands. The pain is burning in character and is induced by warming or exercising the part; or by allowing it to hang down. Rest, elevation of the part or the application of cold tends to relieve the pain. Erythromelalgia has been attributed to vasodilation resulting from some abnormality of the vascular nerves. Lewis finds, however, that the essential abnormality in these cases is not vasodilatation, for, an equivalent degree of vasodilatation may occur in normal subjects in response to warmth or exercise yet pain does not result. Erythromelalgia, or *erythralgia* as Lewis prefers to call the condition, is not of vasomotor origin. The abnormality in these cases is apparently a hypersensitive state of the cutaneous pain fibers to heat or tension. This "susceptible state" of the skin in erythralgia is altogether analogous to that seen in inflammation, and to that which can be induced in any normal person by certain types of cutaneous injury—exposure to ultra-violet light, repeated rubbing or stretching, burns, etc. It is well known that the pain endings of skin injured in these ways are very sensitive to warmth or to tension. Warming the part either by increasing the blood flow through its vessels, or by the application of heat causes burning pain. Pain also results when the part is dependent, the engorged vessels then causing tension upon the hypersensitive nerve endings.

Lewis suggests that in the pain associated with erythralgia and with the types of cutaneous injury just mentioned a chemical substance liberated in the skin serves as the immediate stimulus to the nerve endings. The observation that the pain which follows repeated rubbing or stretching of the normal or of the erythralgic skin is prolonged and intensified by arresting the circulation to the part, supports this conception (p. 270).

ACROCYANOSIS

In this disorder the hands and less commonly the feet are persistently cold, blue and sweaty. Exposure

to cold intensifies the cyanotic color. In the case of the hands the cyanosis commences at about the level of the wrist and deepens as it is traced toward the fingers. There is puffiness of the fingers but trophic disturbances are unusual. The milder forms of the disorder are closely allied, according to Lewis, to chilblains. The disorder is due to increased tone of the cutaneous *arterioles* resulting from hypersensitivity to cold. The condition has not a nervous basis; the fault is in the vascular wall itself, the cyanosis persisting unchanged after anesthetizing the ulnar nerve with novocaine. We have seen that in Raynaud's disease the spasm is of the digital *arteries*. In acrocyanosis the cutaneous circulation is slowed as a result of arteriolar constriction; the partial asphyxia causes capillary dilatation and an increase in the quantity of blood in the skin. The

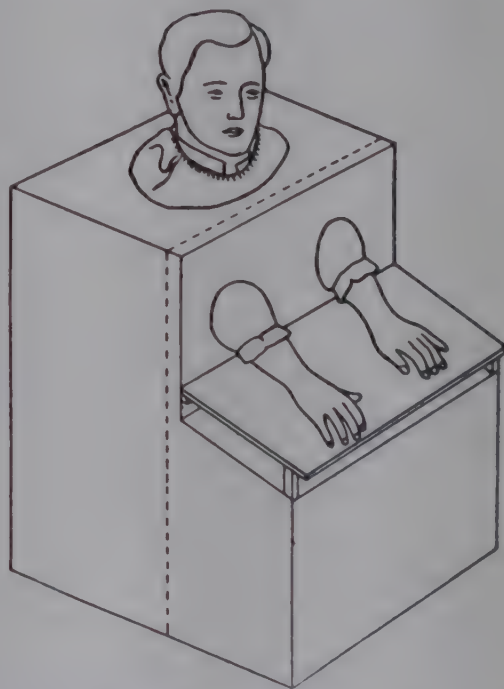


FIG. 115. Warm chamber with subject in position for observing effects in the hands. The neck and forearms pass through canvas sleeves terminating in purse strings. The chamber is divided into two parts at the dotted line. For use with the lower extremities the front wall is made with simple upright front with two appropriately cut outlets for the thighs. (After Lewis and Pickering.)

slower blood flow, by allowing the hemoglobin to give up a greater part of its oxygen store, is responsible for the blue tint of the skin; the depth or intensity of the color is due to the fullness of the vessels (p. 267).

THROMBOANGIITIS OBLITERANS (BUERGER'S DISEASE)

This is an *organic* vascular disease involving the arteries (and to a less extent the veins) of the extremities. The condition in the majority of cases is confined to the lower limbs. The vessels are stiffened and hard. The adventitia is thickened; the media shows atrophy of its muscle and an increase in connective tissue; and, active proliferation of the intima occurs, several layers

of cells being formed. The marked narrowing of the vascular lumen which results is followed by thrombosis. This and not the intimal proliferation itself is responsible for the final obliteration of the vessel. Organization of the thrombus, i.e., its invasion by fibroblasts and its conversion into fibrous tissue, follows. Some restoration of the circulation through the vessel may occur later as a result of the formation of new channels within the substance of the organized thrombus; but whether or not this does follow the blood supply to the part is greatly reduced.

Among some of the earlier manifestations of the condition are: fatigue of the limbs upon erection; intermittent claudication; hypersensitivity of the vasoconstrictor reactions of the extremities to cold resulting in attacks of pallor or cyanosis, coldness and numbness or a dull ache. A definite reduction in blood flow through the part may be demonstrated by the calorimetric method of Stewart (p. 149). Extreme variations in the color of the limb result from altering its position in relation to the level of the heart; when the affected member is dependent undue redness or cyanosis results, whereas when raised above heart level it becomes intensely pale and waxy in appearance.

As the pathological changes progress the pulse disappears from the wrist or ankle, or even from the popliteal or brachial artery; ulcers and other trophic disorders appear and ultimately gangrene of the toes or fingers sets in, requiring amputation. The vascular obliteration tends, however, to creep upwards necessitating amputation at successively higher levels.

The cause of the disease is unknown; some believe it to be of infective origin. Excessive use of tobacco is strongly suspected of being a predisposing factor. Buerger and others have remarked upon the very high incidence of the condition in the Jewish race; of a series of 150 cases reported by Brown and Allen from the Mayo Clinic over 50 per cent were Hebrews. The disease occurs almost exclusively in males, whereas Raynaud's disease with which it is likely to be confused, especially in its early stages, affects females predominantly. Another feature distinguishing it from Raynaud's disease is that in the latter, the color of the skin is affected little or not at all by elevation of the limb; and the pulse in the larger arteries does not disappear. It is possible that spasm of the vessels as a result of hyperactivity of the vasomotor nerves is the initial abnormality in thromboangiitis obliterans. The constriction of the vasa vasorum, it is conceived, may, by

interfering with the nutrition of the arterial wall initiate the characteristic structural changes.

It is, of course, only during the earlier stages of the condition, i.e., when spasm due to increased vasoconstrictor reactivity is a contributing factor and before organic changes have progressed to the point where they have occluded the vessels that treatment of any sort can be expected to bring about any real benefit. When a spastic factor can be demonstrated sympathectomy frequently results in very notable improvement. Even when the larger arterial vessels are obliterated sympathectomy, by removing the vasoconstrictor tone of collateral vessels, may be followed by a definite improvement in the blood supply to the part.

There are several methods to choose from for the detection of vascular spasm. The temperature of the part may be taken by means of a skin thermometer or a thermocouple before and after one or other of the following procedures, which, normally, cause vasodilatation and raise the temperature of the part. (a) Heating the entire body, with the exception of the head and the affected part itself, in a cabinet (fig. 115). (b) The induction of fever by the injection of a foreign protein, typhoid vaccine. (c) Spinal anesthesia which temporarily paralyzes the vasoconstrictors. (d) Anesthetization of a peripheral nerve. (e) The intravenous injection of hypertonic saline by increasing the blood volume will tend to cause a compensatory vasodilatation. A rise in temperature of the part, following one of these procedures, indicates the previous existence of a spastic element. The greater the degree of spasm the more pronounced and rapid is the temperature rise. If the occlusion is entirely organic in nature no change in temperature results.

Instead of recording the skin temperature the blood flow through the affected part may be estimated by the calorimetric method before and after one of the procedures just enumerated.

Cervical rib may cause changes in the circulation of the upper extremity not unlike those due to thromboangiitis obliterans. The subclavian artery tends to be compressed between the bone and the scalenus anticus muscle with consequent reduction in the volume of the pulse of the affected side. But the peripheral vascular disturbances are due mainly, according to the view of Stopford and Telford, to the pressure of the supernumerary rib upon the vasoconstrictor fibers in the lowest trunk of the brachial plexus. Sensory and motor phenomena as a result of pressure upon the somatic fibers also sometimes occur. Constriction of the vasa vasorum with consequent interference with the blood supply of the vascular wall has been suggested as re-

sponsible for the structural changes which ultimately lead to thrombosis and occlusion of the arterial lumina. Lewis, however, dissents from this view. "Why," he asks, "if pressure upon nerve fibers is the cause of the vascular condition, are the effects always of an irritative nature (vasoconstriction)?" "Why do not paralytic manifestations (removal of vasomotor tone with consequent vasodilation) appear at some later stage?" He suggests that the blocking of the peripheral vessels is of embolic origin due to pressure injury of the subclavian artery, and the formation upon its wall of thrombi which are whisked away in the blood stream from time to time.

INTERMITTENT CLAUDICATION

(*claudicare*, to limp)

This is a condition (described by Charcot in 1856) in which, as a result of organic narrowing of the arteries of a limb and consequent restriction of its blood supply, severe pain is experienced in the muscles during exercise. The pain has been attributed to a muscular cramp or to spasm of the vessels. Neither of these explanations can be entertained, for the muscles are flaccid during the attack; the abnormal stiffness of the arteries seems to preclude the possibility of their being narrowed appreciably by spasm; and the smaller vessels are in all likelihood dilated rather than constricted during the attack.

The essential cause of intermittent claudication is a relative anoxia of the muscles—they are called upon to perform work for which the oxygen supply is inadequate. Lewis has shown that pain identical in character with that occurring in this condition can be induced by exercising any normal limb during the arrest of its circulation. When the circulation is restored, an immediate increase in the volume of the limb occurs which is taken to indicate that the vessels were dilated during the pain. In a patient suffering from the disease in one limb it was shown that the pain occurring in the limb during exercise was practically the same with regard to its time of onset, development and duration as that induced by exercising the sound limb during circulatory arrest.

The fundamental importance of anoxia in the production of the pain is also evident from the observations of Pickering and Wayne who found that exercising the muscles of an anemic subject, in whom there was no evidence of arterial disease, caused the characteristic pain of intermittent claudication. Kissin also showed that exercise performed by normal persons during anoxia

(induced by breathing an air mixture containing a low percentage of oxygen) caused the typical cramp-like pain. The clinical experiments of Lewis indicate that the direct cause of the pain is not oxygen lack itself but the stimulation of sensory nerves by the metabolic products of muscular activity. Ordinarily these are removed by oxidation, but they accumulate when the blood supply is inadequate. He refers to the pain stimulus as "factor P." The evidence supporting this conception is as follows:

(1) The pain does not vary with the individual contractions but is a steady ache.

(2) Using a standard test (maximal grip exerted by by thumb and index finger, recorded isometrically, and repeated at the rate of one per second) it was found that in normal subjects with the circulation to the arm arrested, the pain commenced in about 35 seconds after the commencement of the exercise and took another 53 seconds to reach the point where it became intolerable. The pain disappears within 3 seconds after restoring the circulation—presumably as a result of the removal of "factor P." If, on the other hand, occlusion of the vessels is maintained, the pain persists.

(3) Lewis found that the time of onset of the pain is determined by the total amount of work performed rather than by the length of the exercise period. Thus, when the circulation of a normal limb is arrested, pain ensues after the same number of contractions of equal strength whether they are repeated in rapid or in slow succession. On the other hand, if a constant rate is maintained the pain follows sooner with strong than with weak contractions. If, however, the circulation to the part is only partially obstructed (Katz, Lindner and Landt) or if air containing a low percentage of oxygen is breathed (Kissin), the amount of work necessary to cause pain is lessened by increasing the rate at which the contractions are repeated—the chemical factor presumably accumulating more rapidly as a result of the shorter time intervals allowed for its removal.

(4) If, after the pain has been relieved by restoring the circulation to the part, the vessels are again occluded and the limb exercised, the time of onset of the pain ensues earlier, the shorter the period during which the blood had been permitted to flow. This result suggests that products accumulated during the previous exercise period, if not given sufficient time to be removed, are carried over to the second period; the concentration necessary for stimulation is, therefore, reached sooner.

The nature of the chemical pain factor is unknown; Katz and associates believe it to be acid in character and non-volatile. The ingestion of sodium bicarbonate was found to increase the amount of exercise required to cause pain.

The pain in angina pectoris is generally believed

to be produced through a mechanism essentially the same as that causing pain in intermittent claudication.

WOUND SHOCK—CLINICAL AND PHYSIOLOGICAL CONSIDERATIONS

That state of collapse which follows two, three or four hours after a severe tissue injury is variously spoken of as *wound, traumatic, surgical* or *secondary* shock. It is a condition quite distinct from the so-called *primary shock* which supervenes immediately after an injury. Primary shock has a nervous basis; pain and psychic factors, through their effect upon the vascular system, play a prominent rôle.

Secondary, or surgical shock is characterized by a profound fall in blood pressure; pallor and coldness of the skin; cyanosis of the finger tips and lobes of the ears; sweating; fall in body temperature and of the metabolic rate; rapid shallow breathing; small, rapid pulse; apathy: and other manifestations of collapse. Further investigation of a patient or animal in shock will usually reveal marked reduction in the circulating blood volume, even though no hemorrhage has occurred. In very severe cases the systolic blood pressure may be no more than 60 mm. Hg. There is a rise in non-protein nitrogen of the blood, and a fall in the alkali reserve.

When the chest of an animal in deep shock is opened the heart is found to be beating vigorously. The cause of the low blood pressure is, therefore, not of cardiac origin. The heart cavities, however, are incompletely filled. The great veins are depleted of blood, the venous pressure is low, the cardiac output reduced and the circulation through the peripheral vessels slowed.

Slowing of the peripheral blood flow and reduction in the cardiac output occur early in shock and precede the fall in blood pressure.

There is constriction of the arterioles of the splanchnic and cutaneous areas. This is probably a compensatory reaction—a response of pressor mechanisms (e.g., sinus and aortic nerves, p. 240, 241) to the underfilled state of the vascular system.

Inasmuch as many observers have reported an increase in the corpuscular concentration of the blood, or *hemoconcentration* as this has come to be called, it has been the general belief that an essential and fundamental feature of secondary shock is the leakage of plasma from the capillaries as a result of an undue permeability of their walls. But the loss of plasma through excessively permeable vessels remote from the injured region has

yet to be proved. In animal investigations into secondary shock (as produced by mechanical trauma) hemoconcentration to a degree which would indicate any great reduction in blood volume due to plasma loss is by no means a general finding. Furthermore, no direct evidence of plasma loss into the tissues generally has been secured, and even when hemoconcentration exists there is some indication that plasma is removed from the general circulation by becoming "locked up" or pocketed in the minute peripheral vessels rather than by leakage from the vascular system.

Widespread capillary dilatation is a factor which has been generally thought to be present in and largely responsible for the shock state. A considerable body of evidence can be cited in support of this belief. Morrison and Hooker observed an increase in the volume of an intestinal loop when shock supervened, and Mann found that, whereas about 24 per cent of the blood volume of a normal animal is held in peripheral vascular areas and the remaining 76 per cent in the heart and larger vessels, in shock (produced by exposure and handling of the abdominal viscera) 61 per cent was contained in the peripheral vessels.

Pooling of blood in peripheral vascular areas could quite conceivably account for the main features of shock. Any great enlargement of the capillary bed would alone cause a fall in blood pressure without any loss of blood from the vascular system. The maintenance of the normal arterial blood pressure (p. 121) depends upon a nice adjustment of the capacity of the vascular system to the volume of blood. Variation in either factor would have practically the same effect upon the blood pressure.

Moreover, a reduction in the effective or circulating blood volume would be expected to result from any great dilatation of capillary areas. Pooling of blood at the periphery of the vascular system would, by reducing the venous return, deprive the heart of an adequate volume of blood to maintain the blood pressure at its normal level. It may be mentioned in support of this conception that Erlanger has described the packing of corpuscles in the dilated capillaries of the intestinal villi in shock. In the shocked patient, also, slowing of the peripheral circulation is evident from the unusually slow return of color to the skin after blanching, as by the slight pressure of one's finger. It should be pointed out that determination of the blood volume by indirect methods fails to distinguish between a reduction

of blood volume due to actual loss from the vascular system and a reduction of circulating blood volume. In other words, blood which has become sequestered in vascular areas out of general circulation is not included in blood volume estimations by the usual methods.

THEORIES CONCERNING THE PRIMARY CAUSE OF WOUND SHOCK

Many theories have been advanced in attempts to explain the genesis of the shock state. Among those which have found favor from time to time with different groups of workers are the following: exhaustion or paralysis of the vasomotor center as a result of its bombardment by sensory impulses from the traumatized tissues (Crile); "blowing off" of carbon dioxide (acapnia) due to stimulation of the respiratory center by afferent impulses arising in the injured part, or during the hyperpnea of the early stages of general anesthesia (Y. Henderson); multiple pulmonary emboli caused by the liberation of fat globules from damaged bone and subcutaneous tissues (Porter); adrenal exhaustion; etc. None of these theories has stood the test of critical investigation. There is no evidence that the activity of the vasomotor center is depressed in shock. It has been mentioned that arteriolar constriction rather than dilatation occurs, and Porter found that the vasomotor reflexes, both pressor and depressor, were unimpaired in the shocked animal. Nor is acapnia or alkalosis present in traumatic shock. Acidosis is more likely to appear, though not in a causative rôle, the reduced circulation rate and consequent anoxia of the tissues resulting in the accumulation of fixed acids. Porter's fat embolism theory has not been substantiated. Swingle and his associates have directed attention to the very close similarity between the effects of adrenal (cortical) excision and the shock state (p. 694). Low blood pressure due to plasma loss, and collapse are prominent features following suprarenalectomy. The effects of this operation are, however, much slower in onset (several days) and there is no direct evidence that deficiency of the hormone of the adrenal cortex is a factor in the causation of traumatic shock. Moreover cortin is of very uncertain benefit in traumatic shock. With regard to the adrenal medulla, in Cannon's view this part of the gland is more likely to be overactive than deficient in shock (p. 261).

The foregoing theories are given mainly for their historical interest. Today, opinion is divided between two schools. (a) One of these believes that a toxic agent formed in the injured tissues is carried in the blood stream and exerts a widespread effect upon the vascular system. This is the *toxemic theory* of shock. (b) The other school holds that the loss of circulating fluid into the

damaged parts is the major factor. This will be referred to as the *theory of local fluid loss*.

The toxemic theory of shock

As a result of the investigations of a number of workers into the shock state, as seen in wounded soldiers in the war of 1914-1918 or as produced experimentally in animals, the theory arose that the main features were due to the action of a depressor substance formed through the destruction of tissue, especially of muscle. A few years before the last war Dale and Laidlaw had reported upon the action of *histamine*. Struck by the resemblance of the effects of this amine to certain features of traumatic shock, Dale, Laidlaw and Richards in 1919 re-investigated its actions. When injected into animals in doses of 1 mg. per kilogram of body weight, histamine exerts a profound depressor effect upon the circulation, namely, a fall in blood pressure, due to peripheral vascular dilatation. Increased capillary permeability with consequent transudation of plasma from the vessels is also a well recognized action of histamine (p. 269). The fall in blood pressure is, of course, the outstanding feature of shock. Vasodilatation and increased capillary permeability leading to reduced plasma volume were (upon the assumption that the blood pressure fall was due to histamine or a histamine-like substance) supposed to exist as well. The reports of hemoconcentration and a reduction in blood volume in shock seemed to confirm these suppositions. Certain clinical observations were also in accord with a toxemic theory; a tourniquet applied to a damaged limb, for example, appeared to postpone the development of shock, presumably because a toxic substance was prevented from entering the general circulation. It was also generally conceded that amputation of a contused and lacerated part favored recovery from shock, arrested its further development or tended to prevent its onset. Moreover, injury to muscle, which it was presumed was relatively rich in vasodilator substances such as histamine, was especially likely to be followed by shock.

Thus, the toxemic theory of shock in which a histamine-like substance, or histamine itself, was the responsible agent seemed well authenticated and seemed to be finally established by the experiments of Cannon and Bayliss. These observers crushed the limbs of animals and reported that a fall in blood pressure did not result so long as the vessels of the injured part were occluded, though the nerve trunks remained intact. Upon restoring

the circulation a fall in blood pressure occurred. Division of the nerves, on the other hand, without arrest of the circulation in the limb did not prevent the onset of shock.

Others who have repeated Cannon and Bayliss' experiment have not been able to obtain the same results; some indeed have reported findings quite the reverse. Simonart, for example, traumatized a hind limb after occlusion of the vessels, and section of the sciatic and femoral nerves. Shock did not occur when the vessels were released. If, however, the innervation of the limb remained intact, shock ensued even though the circulation had been arrested. Nor has any worker been able to demonstrate the presence of a substance in the venous blood coming from a traumatized limb which would, when injected into a normal animal, induce the shock state. Parsons and Phemister found that the fluid from the injured part failed even to lower the blood pressure of another animal.

It has been suggested by Scudder and his associates that potassium derived from disintegrated cells of the injured tissues is the responsible toxic factor. The blood potassium may rise to double or more than double the normal value in shock, especially in the later stages. Nevertheless, potassium does not appear to be a primary or major factor in the development of the shock state. Manery and Solandt found that the fatal level of blood potassium was many times higher than that seen in animals dying of shock.

The theory of local fluid loss

The toxemic theory of shock has been seriously questioned within recent years, notably by Blalock and his associates, by Parsons and Phemister, by Simonart of Belgium and several others. Blalock claims that the reduction in blood volume and consequent fall in blood pressure can be entirely accounted for by the escape of blood or of plasma from the vessels *at the site of the trauma*. He concludes that a circulating toxic substance does not exist and that transudation of fluid from vessels beyond the tissues directly injured does not occur. He bases his conclusions upon the finding that after bruising a limb by beating it with a hammer the quantity of blood fluid which accumulates within the part, as estimated by comparing its weight with that of the sound limb, is sufficient to cause the fall in blood pressure. In some experiments as much as a third or a half of the total blood volume was calculated to have entered the traumatized area. The loss of this amount of circulating fluid in itself is sufficient to cause death. From their results Blalock and his

followers conclude that there is no essential distinction to be drawn between shock and hemorrhage.

A discussion of the foregoing theories. Several types of injury lead to a condition of falling blood pressure and collapse which we know by the name of secondary shock. Many observers have gone on the assumption that this state, as seen clinically and as produced in animals by different means, has a common underlying cause. This is probably far from the truth. The mode of production of the shock state may be quite different according to the type of injury (mechanical, thermal, etc.). Since the end result, i.e., the state of shock, when fully developed is so similar as judged by the criteria at our disposal, it becomes necessary in any discussion as to causation to specify the type of injury which has been sustained. The present discussion is concerned solely with shock caused by mechanical trauma.

Decisive evidence for either of the theories outlined in the last two sections is lacking. In order to prove the toxemic theory it would be necessary to obtain from the injured tissues or from the blood issuing from them, a toxic substance which upon injection into a normal animal would reproduce the main features of shock. Such evidence has not been secured. Attractive in its simplicity as is the theory of local fluid loss, it fails to conform to several facts. It is true that in many instances the quantity of circulating fluid lost locally is sufficient to reduce the blood volume to the fatal level, but in other instances the fluid lost locally is *not* sufficient in amount to account for death. An animal may die after a mechanical injury with a fluid loss considerably less in amount than that which would be expected to be lethal, had the loss been due to frank hemorrhage. Such instances weigh more heavily against the theory than the other cases argue for it. In other words, the loss of an amount of circulating fluid locally which in itself could be taken as the cause of death does not exclude the possible co-existence of another lethal factor, and when death occurs with a fluid loss *less* than that which would prove fatal if lost by external hemorrhage, then another factor must be sought. There appears to be a "shock factor" quite distinct from the effect of the local loss of circulating fluid.

If it were true that the mode of death in shock and in hemorrhage are essentially and fundamentally the same, blood transfusion should prove equally effective in both conditions. On the contrary, whereas the fall in blood pressure due to hemorrhage is quickly restored to normal by

blood transfusion and is usually well maintained, in shock due to mechanical trauma the beneficial effects of transfusion are as a rule of short duration. The blood pressure is restored for a time but declines again to the shock level. The contrast between the effects of transfusion in hemorrhage and in shock has been pointed out by Moon as well as by several other observers, and has been observed by Taylor and Moorhouse in animal experiments. Taylor and Drummond, from observations upon wounded soldiers in France during the first World War have stated that only those in whom hemorrhage was a major factor gave a satisfactory response to transfusion. In cases of shock accompanied by little hemorrhage, transfusion was not of much benefit. Another difference between hemorrhage and shock is that in the former, dilution of the blood follows promptly, whereas in the latter the tendency is towards hemoconcentration. Attention has been drawn to other dissimilarities between the two conditions by Moon.

A dogmatic statement as to the fundamental cause of shock following mechanical injury is not warranted at the present time. Hemorrhage either external or into the damaged tissues is undoubtedly a contributory factor in many instances, in others nervous influences may play a part. Though it has been difficult to obtain direct evidence of a circulating toxic agent, the possibility if not the probability of such being responsible cannot be ignored.

A consideration of possible nervous factors in the development of traumatic shock

Cannon, though not discarding the toxemic theory, agrees that all cases of secondary shock cannot be so explained. He suggests that in certain instances the primary cause is overstimulation of the sympatho-adrenal system by sensory nerve impulses. Freeman, working in Cannon's laboratory, found that the continuous injection of adrenaline in physiological dosage (0.001 to 0.006 mg. per kilogram of body weight per minute) over a period of two hours caused a fall in plasma volume of from 10 to 29.5 per cent. A reduction in blood pressure to considerably below the normal level occurred upon stopping the injection. Adrenaline, as we know, causes vasoconstriction of the splanchnic and cutaneous areas and dilatation of the vessels of the skeletal muscles (p. 686). The prolonged arteriolar constriction in the cutaneous and splanchnic areas, it is conceived, by inducing asphyxia of the capillary walls renders them more permeable. The vasodilatation in the muscles by increasing the capillary filtration pressure will increase transudation of fluid in these situations. Other conditions, such as "sham rage," which excite the sympatho-adrenal mechanism were also found to

reduce the blood volume (by from 11 to 35 per cent) and cause a fall in blood pressure (to 60 mm. Hg). Sham rage induced after the removal of the sympathetic chains does not cause either a reduction in blood volume or a fall in blood pressure.

The experiments of Simonart mentioned above also indicate a nervous factor in the development of shock. The researches of O'Shaughnessy and Slome point in the same direction. These workers, while unable to obtain any evidence for the existence of a circulating toxin, found that blocking the nervous pathways by spinal anesthesia delayed or prevented the onset of shock in animals whose limbs had been traumatized. They, therefore believe that, though blood loss into the injured tissues plays a part in the development of shock, nervous influences dominate the picture.

The *treatment* of traumatic shock resolves itself into a correction of the abnormal physiology indicated in the foregoing discussion, namely, the restoration of the circulating blood volume by blood transfusion, the administration of fluids and the protection of the patient from cold, pain, anxiety and apprehension. Overheating the patient by means of hot water bottles or radiant heat is to be avoided since it induces dilatation of superficial vessels and thus increases the capacity of the vascular bed. The use of agents, e.g., pituitrin, which constrict the capillary vessels, is indicated. Adrenaline is of little or no value; its effect is evanescent and is exerted mainly on the arterioles whose tone in shock is already high.

Burn shock. An extensive burn may cause death from primary shock which follows almost immediately after the injury has been received, from secondary shock which supervenes in from 2 to 6 hours after the burning, or from toxemia which develops in from 48 to 72 hours. We are concerned here only with the cause of secondary shock due to burns.

An outstanding feature of burn shock wherein it differs from shock caused by mechanical injury is the extreme degree of hemoconcentration which occurs as a result of plasma lost from the burned surface and into the tissues surrounding the burn. In an extensive burn, according to Underhill, 70 per cent of the total plasma volume may be lost from the circulation within a few hours. The shock state following burns is attributed by many observers largely to the reduction in blood volume and to the increased viscosity of the blood. Harkins estimated the fluid loss by burning one side of an animal while it was on a weighing device which tipped towards the burned side as fluid accumulated. The average amount of fluid lost as measured in this way was 2.2 per cent of the body weight. The increase in weight of the

burned side commenced almost immediately following the burning and continued at a rapid rate for some time. The blood pressure, however, remained near the normal level until a short time before death, when it collapsed rather suddenly.

The question of a *toxic factor* in burn shock is confused for the reason that a distinction has not always been drawn between the stage of shock and the later stage of toxemia which results from the absorption of proteolytic products derived from the burnt tissues or of bacterial origin. Robertson and Boyd were among the first to investigate the question of a burn toxin. They reported that an alcoholic extract of burned skin but not of normal skin contained a toxic agent which caused death when injected into normal animals. The blood or red cells, but not the plasma, of burned animals also contained the toxic agent. They concluded that a toxin formed in the burned tissues was absorbed into the blood stream and carried by the red cells. Vogt also reported that if a burned area of skin from one animal (guinea pig) were excised and transplanted to another, the first animal survived but the second died. This experiment, however, as well as those of Robertson and Boyd, is pertinent rather to the question of burn toxemia which occurs at a later stage than to the development of shock itself. The finding of a high concentration of histamine in the blood of burned patients has revived the question of a toxic factor in burn shock. Barsoum and Gaddum determined the histamine concentration of the blood in a number of patients suffering from extensive burns and found it several times higher than the normal. However, no clear correlation in time between the histamine concentration in the blood and the onset of shock was found. Rose and Brown observed that the course of the blood histamine concentration following burns could be divided into three stages, (1) an early increase; this was not invariable, (2) a marked decrease during the period of edema and plasma loss, i.e., *during the stage of secondary shock*, and (3) a return to normal or above normal as the edema subsides and the patient is improving. It would not appear from these results that histamine is the responsible agent in the development of shock following burns.

Certain changes found at autopsy in burned subjects, e.g., damage to liver and kidney and intestinal ulceration have suggested a toxic factor to many, but such findings are probably associated with the toxemic stage rather than with the stage of shock.

The most effective measure for combatting burn shock is the transfusion of large volumes of plasma or serum (up to 5000 cc. in 24 hours) or a suitable substitute, with the object of restoring the blood volume and coincidentally of reducing the hemoconcentration. Benefit has been reported by some observers (e.g., Wilson; Rhoades; Lee and their colleagues) from the use of adrenal cortical extracts. The cortical hormone is said to decrease capillary permeability and thereby to reduce the plasma loss.

The "Crush syndrome." A person who has had a limb held and compressed for some hours by a heavy object such as a beam or a pile of rubble may pass into a state resembling shock some time after he has been released and removed to hospital. A number of such cases have been reported in England following air raids. But a closer study has revealed that they do not present the typical features of wound shock; death has been due to uremia. The part after its release may not appear to be severely damaged and the patients seemed at first to do well after reaching hospital. Marked edema of the limb developed later, accompanied by oliguria. The urine is brownish in color and contains dark granular casts; it gives the benzidine reaction due to the presence of myoglobin (p. 43) derived from the damaged muscles. Complete suppression of urine ultimately supervenes. The condition has been studied by Bywaters and his associates, who attribute the renal effects to blockage of the tubules of the kidney by myohematin. The anuria is therefore caused in a manner analogous to that resulting from the transfusion of incompatible blood (p. 35), the difference being that in one the pigment is liberated from muscle, in the other from hemolysed erythrocytes.

Attempts to reproduce the "crush syndrome" in animals have not been entirely successful. When both hind limbs of an animal such as the dog are made ischemic by compression for three or four hours and the limbs then released, the parts become swollen and a steady fall in blood pressure follows. Death occurs within a few hours. There is a rise in the non-protein nitrogen of the blood and there may be the passage of blood-stained urine before death. In experiments upon cats Eggleton found that an extract prepared from the affected muscles caused impairment of renal function (reduction of creatinine clearance) when injected into normal animals.

Blast injury. The explosive blast of a bomb or shell may cause death without any sign of external injury. But hemorrhages into the lungs, beneath the pleura or into the tissues of the liver and other abdominal viscera may be found at autopsy. Actual laceration of pulmonary tissue or of the abdominal organs may occur. The effects of blast have been studied experimentally by Barcroft and by Zuckerman. Barcroft attributes the pulmonary trauma to the sudden distension of the lungs and the rupture of the lung tissue

by the blast of air caused by the explosion. Zuckerman believes it to be due to the impact of the percussion wave set up by the explosion upon the body surface. The first theory does not explain the abdominal lesions that are so frequently observed. Nor is the second theory able to explain satisfactorily the pulmonary lesions, for one would expect the thoracic walls to protect the lungs from the force of the blast. It is probable that, in most instances, both factors play a part in blast injuries.

Anaphylaxis, Anaphylactic shock

The anaphylactic reaction is one which follows the administration of a foreign substance (most frequently protein in nature) to an animal which has been sensitized to it by a previous dose. It is one of the manifestations of an antigen-antibody response. In the dog and guinea pig, an interval of from 12 to 14 days must elapse between the two doses, in order that the maximum effects of the second dose may be produced.

The anaphylactic reaction, which in its severer manifestations is called anaphylactic shock, shows pronounced species differences. *In the dog* it is marked by dyspnea, vomiting, diarrhea, salivation, a profound fall in blood pressure ending in circulatory failure and death. The hepatic veins are strongly constricted, the liver and intestinal vessels are engorged and there is an increased flow of lymph from the thoracic duct. The blood is incoagulable as a result of the liberation of heparin from the liver (Markowitz and associates). The histamine content of the liver of sensitized animals is increased, but is reduced below the normal in anaphylaxis. Thus, the major symptoms of anaphylactic shock in the dog are centered in the liver. Nevertheless, many of the features of anaphylactic shock can be produced in the hepatectomized dog. *In the guinea pig*, the anaphylactic reaction consists of a powerful contraction of the muscles of the bronchioles. There is extreme dyspnea; death is due to asphyxia. The effect can be demonstrated in the perfused isolated lungs of a sensitized animal by the addition of the antigen to the perfusion fluid. The histamine content of the blood and lungs is increased to several times the normal.

In the rabbit, the reaction may be general or purely local. When the foreign substance is injected subcutaneously, the skin and subcutaneous tissue at the site of the injection become edematous and swollen; a sterile abscess or slough appears. This was originally described by Arthus and is known as the Arthus phenomenon. When the antigen is administered intravenously, the blood pressure falls abruptly, the respirations become rapid, but there is no dyspnea. The bladder and intestine are evacuated. The animal may die within a few minutes from dilatation and failure of the right ventricle. The failure of the heart is secondary to the increased resistance in the pulmonary circuit caused by constriction of the arterioles. The arterioles in other parts of the vascular system are also constricted and emboli composed of clumps of leucocytes may be

seen blocking the pulmonary and systemic capillaries. This, no doubt, accounts for the leucopenia which is found in the peripheral blood stream.

The evidence indicates, with little doubt, that the antibody-antigen reaction takes place in the tissue cells and not in the blood plasma. Dale showed, for example, that when the uterus was removed from a sensitized guinea pig and its vessels freed from all traces of blood, it gave the typical anaphylactic contraction, when the antigen was added to the bath in which it was immersed. Manwaring also found that the blood of the sensitized animal could be replaced by blood from a normal animal without affecting the first animal's sensitivity. Sensitivity can be passively transferred by the injection of the serum of a sensitized animal into a normal animal. A latent period elapses between the injection and the development of the passive sensitization which is presumably required for the fixation to the tissue cells of the antibody transferred in the injected blood. The interval of from 12 to 14 days, as mentioned above, which must elapse in order for the maximum effects of the antigen to become manifest is used, presumably, for the production of the antibody and its attachment to the tissue cells.

It is now generally accepted that the antigen-antibody reaction in some way brings about the liberation of histamine by the affected tissues and that the action of this amine is responsible for the anaphylactic manifestations. Practically all the features, as seen in these three species, can be explained upon such a basis. In the dog and guinea pig, the anaphylactic reaction is associated with a rise in the histamine concentration of the blood and, although the whole blood of the rabbit shows no increase and is often reduced, the amine passes from the white cells (which contain it in especially large amounts) into the plasma. The species peculiarities of the anaphylactic manifestations can be accounted for largely by the amount of smooth muscle in the reactive tissues of these three species and by its susceptibility to the action of histamine. In the dog, the smooth muscle of the hepatic veins is especially well developed. In the guinea pig, the bronchioles are particularly susceptible to stimulation by histamine and, in the rabbit, the pulmonary arterioles show unusually thick muscular coats.

Peptone solution, injected intravenously, produces in the dog effects almost identical with those of anaphylactic shock, including incoagulability of the blood due to the liberation of heparin by the liver. Sensitization by a previous dose is not necessary, however. In man, fatal anaphylactic shock may follow the injection of horse serum into a person who has been sensitized by a previous administration. Allergic reactions, in general, show many similarities to anaphylactic reactions and many observations suggest that the two are fundamentally allied, although in the case of allergic reactions, sensitization by an earlier exposure is apparently not required, the reaction appearing upon the first known contact with the foreign substance.

CHAPTER XXVIII

SPECIAL FEATURES OF THE CIRCULATION IN DIFFERENT REGIONS

THE CAPILLARY CIRCULATION

The term *capillary vessels* will be employed to include all the purely endothelial tubing which lies between the arterioles on the one hand and the small veins on the other.

The observations of several investigators in the past have pointed to the capillaries being capable of regulating their size quite independently of the state of the arterioles which feed them. Stricker (1865), for example, saw active contractions and dilatations of capillaries in the nictitating membrane of the frog. Roy and Brown found that individual capillaries lying close together and apparently supplied with blood from a common arteriole required different pressures to obliterate their respective lumina. Steinach and Kahn obtained more direct evidence of independent capillary movements by electrical stimulation of excised tissues (nictitating membrane of the frog and mesentery of the cat). Constriction of individual capillaries was clearly demonstrated. These observers also reported that stimulation of the cervical sympathetic in the living animal caused contraction of the capillary walls in an area *from which the circulation had been occluded*. Scant attention apparently was paid to these observations. Until the more recent work of Lewis and of Krogh and their associates, few physiologists believed that *active* changes in capillary diameters could occur. The capillaries were considered to play a purely *passive* rôle; changes in their capacity were believed to depend entirely upon the distension or collapse of their elastic walls in strict accordance with the diameters of the arterioles at the moment, and consequently upon the quantity of blood which they received from the arterial side.

This view is now admitted to be wrong and the independence of capillary movement is firmly established. The evidence will be briefly cited.

(1) Cotton, Slade and Lewis showed that reddening of the skin of the arm could be induced by mechanical stimulation, after the circulation had been arrested by means of a blood pressure cuff. The dilatation of the superficial vessels, it was argued, must have been the result of relaxation of the capillary wall and not of passive distension, since after the blood in the part had

become stagnant, and venous and arterial pressures equal, arteriolar dilatation would have drained blood from, rather than forced it into the capillaries. A white line was also obtained upon drawing a point lightly over the skin, which would only be satisfactorily explained by capillary constriction. (2) Krogh observed the capillaries in the tongue muscles of the frog beneath the microscope, and showed that they contracted when stimulated mechanically, as by touching them with a stiff hair. Dilatation could be induced toward the venous end of the capillary while the diameter of the arterial end remained unaltered, the dilated vessel filled from the vein. Drawing the hair along the capillary toward the arteriole was followed by a progressive opening up and filling of the former vessel. As the dilatation reached the arteriole the arterial blood was admitted and the flow in the capillary became reversed. (3) When the arteries to the frog's tongue were occluded, active dilatation of the capillaries was induced by mechanical stimulation. If, on the other hand, the capillaries were constricted they remained so, against an arterial pressure of several millimeters of mercury. Lewis also showed that the capillaries of the human skin were capable of remaining contracted against an arterial pressure of approximately 100 mm. of mercury. (4) Various chemical substances, e.g., acids (lactic, CO_2), urethane, iodine, cocaine, silver nitrate and chloroform cause dilatation of the capillaries; some of these, e.g., urethane and iodine, have no effect upon the arterioles. Alkalis and oxygen cause capillary constriction. Though adrenaline (in ordinary dosage) causes constriction of both arterioles and capillaries in man, in the frog the arterioles are constricted while the capillaries are often simultaneously dilated. Histamine induces dilatation of both types of vessels in man but, as shown by Dale and Richards, causes arteriolar constriction and capillary dilatation in the cat. Acetylcholine and adrenaline applied directly to the arterioles cause dilatation and constriction, respectively, yet, during these arteriolar changes, scarcely noticeable alterations in capillary diameters occur.

The results of a sufficient number of experiments have been cited to show that there is no reason for doubting the independent regulation of the capillary circulation.

Spontaneous changes in capillary diameters

Krogh found that there was a great variation in the number of capillaries which might be pervious at a given moment. The number of patent vessels was directly related to the activity

of the tissue at the time, the number of open vessels being much fewer in resting than in active muscle. When, for example, India ink was injected into the vessels and portions of tissue excised before and after excitation, the increase in number of open vessels in the latter instance was very striking. The resting muscle in the intact animal is pale and only relatively few vessels can be seen. Others may be observed to be contracted to such small diameters that a red cell is unable to enter the narrowed channel without

changed, capillaries hitherto invisible, since their lumina apparently had been obliterated by tonic contraction, sprang into view, while other vessels which had been partially closed dilated fully. Krogh considers that these changes play an important rôle in the mechanism for the regulation of the oxygen supply to the tissues. During rest a comparatively large area of tissue is fed with blood from a single central capillary. During activity, as more capillaries become patent, the area of tissue supplied by each vessel becomes correspondingly reduced (see fig. 150, p. 323). Richards also observed a great increase in the number of capillary tufts in the frog's kidney, when the activity of the organ increased (see p. 387). From these observations upon frog's muscle and kidney, conclusions cannot, however, be drawn regarding the blood supply to tissue in general, since Lewis has found that, in the human skin at any rate, the capillary pattern changes very little from time to time; all the vessels are open whether the blood flow is small or large. Lewis concludes that augmentation of the blood flow through the skin is brought about through the greater dilatation of pre-existing channels rather than by the opening of capillaries that had been previously closed.¹

The elements in the capillary wall responsible for their independent movements

Since the capillaries are devoid of muscle fibers, the question naturally arises concerning the means by which their contraction and relaxation are brought about. The endothelial cells themselves, either through actual contraction or by swelling, appear to be responsible for the alterations in capillary diameters. The Rouget cells (p. 112) found in relation to the capillary wall in amphibians are not, as was previously believed, concerned in the reactions. Clark and Clark give evidence for the Rouget cells being simply wandering connective tissue elements which have come to rest upon the capillary wall. They have observed movements of the endothelial wall independently of the Rouget cells, and Florey and Carleton describe cells in mammals which are probably analogous to Rouget cells, but think that they are too few in number to be of any importance in the capillary movements. More-

¹ Bordley and associates disagree with this conclusion, for they observed intermittency of flow in the capillaries of the skin over the tibia. Even two capillaries arising from a single arteriole were seen to alternate with one another in permitting the passage of corpuscles.

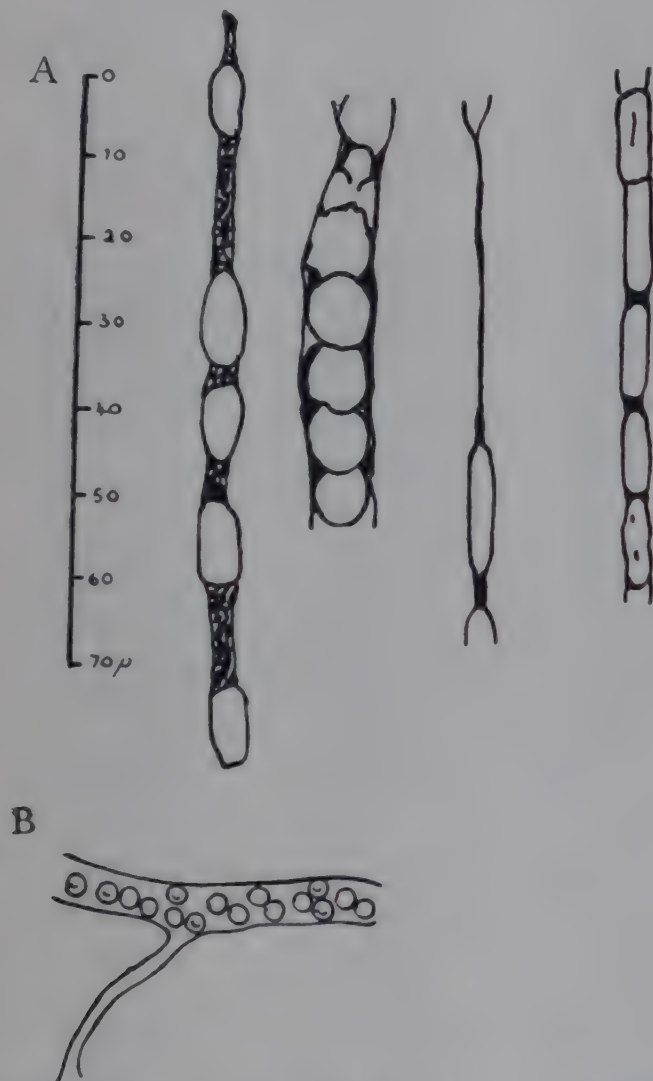


FIG. 116. A, muscle capillaries of guinea-pig vitally injected with India ink. Blank oval areas represent red cells, most of which are distorted in shape. B, illustrates "plasma skimming." (After Krogh.)

becoming squeezed out of shape. A cell pressed into a elongated or sausage-like form could frequently be seen within the vessel or, in some instances, imprisoned by the complete closure of the capillary lumen at each end (fig. 116A). In other instances, constriction of the vessel excludes the corpuscles entirely from a neighboring capillary channel, the plasma alone being permitted to enter. This phenomenon has been termed "plasma skimming" (fig. 116B). Upon stimulating the muscle the picture was entirely

over, they state that a clear space separates these cells from the capillary wall. The Rouget cells are probably reticulo-endothelial elements.

THE INNERVATION OF THE CAPILLARIES

EFFERENT FIBERS. Non-medullated nerve filaments were observed by Woollard accompanying the capillaries. They form a loose investment of the vessels, but none was seen to end actually upon the capillary wall. These nerves are derived from the sympathetic and are extensions from the periarteriolar plexus (p. 232); they degenerate after removal of the sympathetic chain. Physiological evidence for constrictor fibers to the capillaries has been obtained by several workers. The observations of Steinach and Kahn have been mentioned (p. 264). Hooker obtained contraction of the capillaries of the ear upon stimulation of the cervical sympathetic in the cat, which he concluded was a direct effect upon the vessels. Marvin and Harris obtained similar results, but excluded more certainly any possibility of a passive effect upon the capillaries as a result of arteriolar constriction by arresting the circulation to the rabbit's ear before applying the stimulus. Krogh and his colleagues observed contraction of the capillaries of the frog's web when sympathetic fibers were stimulated. Excision of the abdominal sympathetic ganglia, on the other hand, or section of the sciatic, by removing constrictor tone, caused the capillaries of the web to dilate.

Dilatation of muscle capillaries is probably mainly dependent upon the production of acid metabolites, though it is possible that they also, like the arterioles, are dilated through the medium of sympathetic fibers (p. 234).

Engel postulates a permeability-controlling function for the sympathetic based upon experiments in which the vessels of the knee joint were perfused with a dye-containing fluid. Sympathetic stimulation was found to increase, sympathectomy to decrease the excretion of dye into the joint cavity.

AFFERENT FIBERS. Woollard observed *medullated* fibers reaching as far as the arterioles but no farther. They were seen to end by collateral branches in the arteriolar wall on the one hand, and in the adjacent subcutaneous tissue on the other. Some of the latter were seen to terminate in Pacinian corpuscles (p. 801). These medullated fibers are sensory and probably provide the basis for axon reflexes; they probably also convey antidromic dilator impulses from the

central nervous system. Doi, for example, caused full dilatation of the arterioles in the frog by means of acetylcholine; upon then stimulating the posterior nerve roots dilatation of the capillaries was observed. Since the blood flow through the arterioles was already maximal the dilatation could not have been simply a passive effect. This observation has been confirmed by Krogh and his associates who also obtained dilatation of capillaries in the frog's tongue upon mechanical stimulation of the peripheral end of the glosso-pharyngeal. The failure, however, to demonstrate sensory fibers ending upon the capillary wall lends support to the view of Lewis that the dilatation of the cutaneous capillaries is brought about through the intermediary of a chemical substance (H-substance, p. 269) liberated at the nerve ending. Stohr also states that a nerve fiber can be traced to the vicinity of only one out of every hundred capillaries, yet all dilate as a result of nerve stimulation. This, of course, is an indication that vessels more remote from the nerve terminal are acted upon by a diffusible chemical substance liberated by the latter.

THE VASCULAR REACTIONS OF THE HUMAN SKIN

The arterioles of the skin upon approaching the bases of the papillae (i.e., the layer of true skin immediately underlying the epidermis) turn horizontally, lose their muscular coats and give rise to hairpin-shaped endothelial tubes—the *capillary loops*. The proximal or arterial limb of the capillary loop ascends in the papilla and then turns upon itself to form the venous limb. The latter on reaching the base of the papilla joins with the venous limbs of neighboring loops to form a *collecting venule*. The collecting venules anastomose with one another to form a rich plexus—the *subpapillary venous plexus*—which runs horizontally beneath the bases of the papilla. It drains into deeper veins.

The capillary loops, collecting venules and subpapillary venous plexus are formed of simple endothelial tubing and may therefore be referred to as the capillary system of the skin. The walls of the arterioles and deeper venules contain smooth muscle.

The capillary loops, as Lombard first demonstrated, can be seen readily in the living skin under the low power of the microscope. A drop of cedar or paraffin oil is placed upon the skin at the base of the finger nail or other region where the epidermis is thin. The area under observa-

tion is illuminated by a powerful beam of light (fig. 117). If the horny layer be removed by blistering, the vessels are rendered more distinct. Under favorable circumstances the vessels of the subpapillary venous plexus and even deeper vessels may also come into view.

The capillary circulation in relation to the color and temperature of the skin

The color of the skin may afford important diagnostic information, and the factors underlying the variations in the tint and depth of color are of considerable interest from a purely physiological point of view. Lewis has made an extended study of the capillaries of the human skin and their reactions to various types of stimulus. The color of the skin is not dependent normally upon

still be seen; subsequent occlusion of the capillary loops did not increase the pallor appreciably.

When the skin is unusually pale and little blood is contained in the superficial vessels (subpapillary venous plexus) the skin is more transparent, and the deeper venous plexuses then contribute largely to the color of the skin, often adding a leaden tint to the pallor. When the overlying vessels are open and the skin is well supplied with blood these deeper vessels are hidden from view.

Apart from pigmentary effects and assuming the general arterial blood to be normal, the *color* of the skin, i.e., the dominance of the reddish or of the bluish hue depends upon the extent to which the oxyhemoglobin becomes reduced during the passage of the blood through the cutaneous vessels. The degree of reduction will depend entirely, as a rule, upon the rate of blood flow. When the flow is rapid or slow the blood is, respectively, more arterial or more venous in character. The tint of the skin varies accordingly.

The *depth* of the skin color, i.e., its intensity apart from its hue is dependent upon the diameters and the degree of engorgement with blood of the superficial vessels.

So, taking into account both the hue and the depth of color, an intense scarlet color of the skin indicates a normal or increased blood flow and dilated vessels; a deep blue color (see cyanosis, p. 372) accompanies a slowed blood flow and dilated vessels (such as may result from obstruction to the venous trunks). Pallor or a light pink color of the skin is seen when the vessels are constricted or of moderate tone, and the blood flow normal or rapid. A slowed cutaneous blood flow and constricted superficial vessels tend to produce a leaden or ashen type of cyanosis for, as mentioned above, the dark blood in the deeper venous plexuses then becomes faintly visible.

The *temperature* of the skin depends largely upon the rate of blood flow through its vessels. The radiation of the body's heat is carried out principally through the medium of the cutaneous vessels (p. 624). The warmer blood of deeper regions is diverted through the cutaneous channels and becomes cooled in its passage. So the cyanotic skin (due to reduced cutaneous blood flow) is usually cool, and the flushed, scarlet skin hot. But the skin may be pale with constricted superficial vessels and yet radiate a large quantity of heat, if the blood flow through deeper vessels is rapid. Sometimes such a pale skin is hotter than another of a redder color. In the former instance, heat from the swiftly flowing blood



FIG. 117. The bed of the finger nail in a healthy subject, showing the capillary loops and the summits of the skin papillae. The size of the structures is indicated by the $\frac{1}{16}$ mm. scale. (After Lewis.)

the most superficial vessels, i.e., the capillary loops, but upon the subpapillary venous plexus. The vessels of the plexus, though more deeply placed, present a greater area parallel to the skin, whereas the capillary loops are disposed chiefly at right angles to the skin surface. A simple experiment devised by Lewis illustrates the predominant rôle played by the subpapillary venous plexus in determining the skin color. When the superficial vessels were observed beneath the microscope through a glass slide, it was found that as the slide was gradually pressed down upon the skin the venous plexus collapsed first; not until further pressure was applied were the capillary loops obliterated. Blanching of the skin occurred, nevertheless, at the moment when the blood was pressed from the plexus and while the capillary loops could

in the deeper vessels is simply conducted through the overlying skin and dissipated from the surface through radiation and convection.

Vascular responses of the skin to stimulation by mechanical and other agencies

THE WHITE REACTION. If the surface of the skin be stroked lightly with a blunt "pointed" instrument, a line of pallor appears in from 15 to 20 seconds which traces the path taken by the instrument. The line attains its maximal intensity in from a half to 1 minute, and then gradually fades to disappear in from 3 to 5 minutes. This *white reaction* must not be confused with the white trail which follows *immediately* in the wake of the instrument and is due simply to the expression of blood from the vessels by the instrument. The white reaction proper is due to *direct stimulation of the capillary wall and has not a nervous basis*. It has been shown by Lewis to be due to the tension exerted upon the walls of the minute vessels—capillary loops, collecting venules and subpapillary venous plexus—which respond to the stimulus by contraction. The sharply delineated character of the white line, and the fact that it can be obtained after the circulation through the region has been occluded by compression of the larger vessels, show that it is an active capillary response, and not the result of arteriolar constriction. The contractile force exerted by the capillary wall is such that it is capable of resisting a pressure of from 50 to 100 mm. Hg. In other words, the capillaries can remain contracted in the face of any pressure that could normally reach them through the arterioles.

THE TRIPLE RESPONSE. This comprises: (1) *the red reaction*, (2) *the flare*, and (3) *the wheal*.

(1) *The red reaction.* If the pointed instrument be drawn more firmly across the skin, especially of the forearm or back, a red instead of a white band appears after a somewhat shorter latent period (3 to 15 seconds), reaches its maximum in from a half to one minute, and then gradually fades. The time of its disappearance is variable; this may occur in a few minutes or be postponed for half an hour or more. It can be seen to assume a bluish tinge before it fades. Like the white reaction it is strictly localized to the line of stroke; it is due to *dilatation* of the capillaries. The red reaction can be induced in its full intensity in the skin from which the circulation has been occluded, so it is due to active dilatation of the minute vessels and is not a passive result of arteriolar dilatation (see p. 264). By means of a

thermocouple placed upon the red line a rise in temperature indicating increased blood flow may sometimes be detected. *The red reaction is not dependent upon nervous mechanisms since it occurs after section and degeneration of the cutaneous nerves.*

Pale lines bordering the central red band can frequently be seen. These are due to capillary contraction resulting from tension exerted upon the skin on either side of the line of stroke. The white halo is identical in every way, e.g., latency, duration and causation, with the white reaction described above. A certain diagnostic importance, quite unjustified, has in the past been attached to the red reaction with pale borders. It was spoken of as the *tache cérébrale*, or as *Trousseau's phenomenon*, and was believed to signify the existence of certain meningeal or cerebral lesions. It is, however, a perfectly normal response to mechanical stimulation.

(2) *The spreading flush or flare.* If the stimulus is unusually strong, or is repeated often enough, the reddening of the skin is not confined to the line of stroke but surrounds it for a variable distance (1 to 10 cm.) according to the intensity of the injury inflicted. The temperature in the suffused area is definitely raised. This flare reaction appears a few seconds (15 to 30) after the local red line, and fades sooner but remains a bright arterial color throughout. It is due to dilatation of the arterioles, since it does not appear after the circulation of the part has been occluded by means of a tourniquet; also, unlike the red reaction, *the flare is dependent upon local nervous mechanisms (axon reflex)*. *It occurs after the nerves are divided but not after they have degenerated.*

(3) *Local edema or wheal.* When the stimulus is still more intense the skin along the line of the injury becomes blanched and raised above the surrounding area to a height of 1 or 2 mm. or even more. Such a wheal or welt is commonly produced in a normal person by the lash of a whip and other types of strong localized stimulation. The circular wheals of an urticarial rash (hives), are similar in character. In susceptible individuals, even light stimulation, such as drawing a pencil with moderate pressure over the skin of the back, will produce linear wheals surrounded by a diffuse red halo along the pencil's track. In this way letters or other designs may be embossed upon the skin (fig. 118). This phenomenon, which is spoken of as *dermographism* or *facitious urticaria*, has been considered pathological, though actually it can be demonstrated to a greater or less degree in many young and perfectly healthy individuals, and can be elicited

in some degree by repeatedly stroking the skin of the back of almost any normal person.

The wheal is preceded by and completely replaces the usual red reaction. It makes its appearance in from 1 to 3 minutes from the time of injury and is at its maximum height in 3 or 5 minutes. It is surrounded by the flare described above. The raised patch at first is clearly cut, but as time passes it increases in diameter and decreases in height, loses its sharpness and finally, though perhaps not for some hours, disappears. The wheal is due to the transudation of fluid from the minute vessels involved previously in the red reaction; it is, therefore, a localized edema. The gradual reduction in height and sharpness of the wheal and its final disappearance are due to the diffusion of the exuded fluid into a wider area of skin. Sometimes the fluid collects beneath the horny layer of the skin and strips it from the

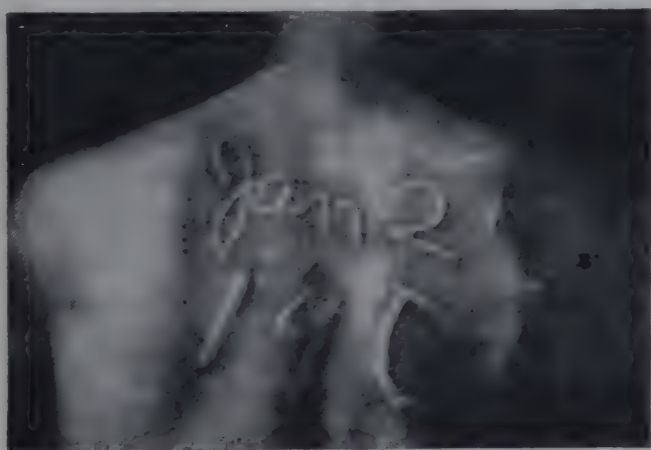


FIG. 118. Dermographism (from Adami's textbook of Pathology, after Hyde and Ormsby).

underlying epidermis. Such a collection of transuded fluid constitutes a blister.

Increased permeability of the capillary wall is judged to be the immediate cause of the localized edema which constitutes the wheal. Increased intracapillary pressure, distension of the capillary lumen or reduction in pressure in extracapillary spaces have been shown by Lewis to be not responsible. Suction, for example, amounting to a negative pressure of 90 mm. Hg, applied to the surface of the skin over the line of the red reaction or over the area of the flare does not cause a wheal to form. Nor will the application of a positive pressure of 50 mm. Hg prevent its appearance. Increasing the intracapillary pressures by compressing the veins does not cause a wheal to form more readily along the track of a red reaction; as a matter of fact a wheal upon a congested area is less pronounced. That increased permeability rather than simply a rise in the filtration pressure, is the dominating feature is also manifest by the high protein content of the transuded fluid. This more nearly approaches that of blood serum than the fluid of ordinary edema.

Wheal production does not depend upon a nervous mechanism. Though an accompanying flare is not an essential feature of a wheal, since the phenomenon can be elicited in denervated skin, the red halo is nearly always present, and in normal skin the degree of whealing is usually proportional to the latter's intensity. When, for instance, the injury is inflicted while the circulation is occluded, so that the flare is prevented, the wheal does not appear until the circulation has been again restored. This simply means, however, that though increased capillary permeability has occurred during the period of occlusion, blood fluid is not available in sufficient quantity for the production of the edematous swelling.

H-substance

A considerable weight of indirect evidence has been presented by Lewis to support the conception that a diffusible substance is responsible for the three reactions comprising the triple response. This material, which he calls *H-substance*, is thought to be liberated by the injured cells of the epidermis lying beneath the horny layer and superficial to the papillae. The possibility that more deeply lying tissues, when subjected to injury, may release the substance is not excluded, but a needle which does not penetrate beyond the epidermis elicits the typical threefold reaction. The chemical substance closely resembles *histamine* in its action. It apparently causes the red reaction and the wheal by a direct action upon the capillary wall. The flare is believed to be due to chemical stimulation of the sensory endings of the skin, thus bringing about arteriolar dilatation through the mechanism of the axon reflex (p. 247).

Though, as just pointed out, the evidence for this theory is indirect and actual proof of the existence of such a humoral mechanism is lacking, the results of Lewis's experiments carry conviction. The reader is referred to this author's original papers or to his monograph for the details of the various ingenious experiments performed, and the clear arguments set forth in support of his thesis. The evidence which has been brought forward can be no more than briefly cited here. The following is a summary:

(1) Histamine (1:1000 histamine phosphate) when pricked into the skin reproduces the triple response characteristic of mechanical injury. The individual reactions, local red reaction, wheal and flare produced by histamine are indistinguishable in all their features from those resulting from the various types of skin injury, pricking, scratching, freezing, burning, etc.

(2) Histamine can be extracted from many tissues of the body including the cells of the epidermis.

(3) An individual in whom the cutaneous reactions were readily produced was chosen and the circulation to the two arms occluded by means of a pneumatic armlet. A minute after circulatory arrest a stroke was made upon one arm, and on the other 9 minutes later. A typical flare resulted in each instance when the circulation was restored to both arms simultaneously. If the flares were due purely to a nervous mechanism, they should both fade at the end of the same interval of time following the application of the stimulus. That is, the second flare should disappear 9 minutes after the first. As a matter of fact they disappeared almost simultaneously. This observation though inexplicable

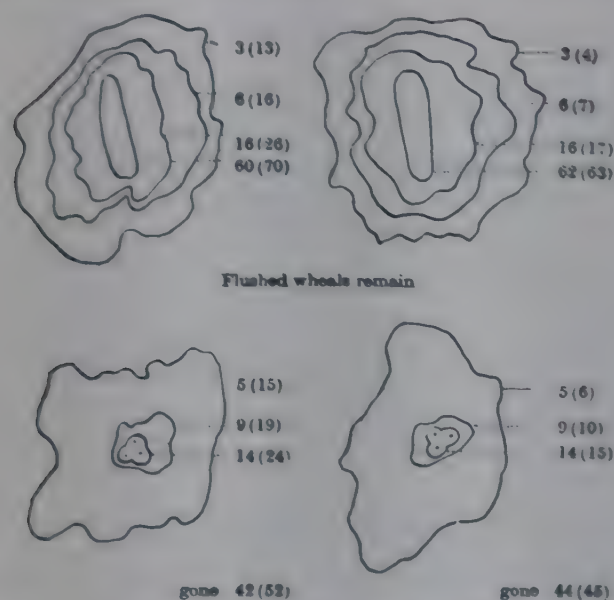


FIG. 119. Reactions caused by histamine and by injury (upper figure) in an urticarial subject. The vessels of the two arms were occluded. One minute later the left forearm was stroked (above) and a group of three histamine punctures (1 in 3,000 dilution) was laid down (below); 9 minutes later the right forearm was similarly and symmetrically treated; the vessels of both arms were released 10 minutes later i.e., at the 11th minute. The numbers outside the brackets indicate the times in minutes at which the contours were outlined after restoration of the circulation. The numbers within the brackets give the times elapsing after application of the stimuli. In the stroke figures the fading was followed until the redness became confined to the wheals. (After Lewis.)

upon a nervous basis conforms with the theory that the responsible agent is a chemical substance released by the injury. It also indicates that the chemical remains at the site of injury, its effect subsiding only after the blood flow to the skin has been restored. It is clear that if the flare is due to a released substance, then the same period of time will be required for the blood to wash away the material from the stimulated point in each arm. Identical results were obtained when, instead of a mechanical stimulus, histamine itself was pricked into the skin (fig. 119).

(4) Two wheals with their surrounding flares were made to appear upon the skin of the arm, one a short distance above the other. An elastic bandage was then wrapped tightly around the arm so as to cover the

lower wheal and the lower half of the corresponding flare. The lower half of this flare was in this way deprived of its circulation while its upper half was visible above the bandage. The entire circumference of the upper flare was beyond the margin of the bandage. The bandage was retained in position for 20 minutes. The upper flare was found to fade gradually and to disappear in the usual length of time. The visible part of the lower flare, however, retained its vivid hue throughout the period of occlusion and only upon removal of the bandage and the re-entry of blood into the lower half of the flare did fading commence. This result is interpreted as indicating that the released substance being retained in the occluded area exerted a persistent effect upon the nerve endings there, and through axon reflexes sustained the arteriolar dilatation in the unoccluded half.

(5) Lewis and Harmer found that when wheals were induced by stroking an extensive area of the back of a susceptible subject, generalized circulatory responses similar to those resulting from the hypodermic administration of histamine, namely, flushing of the face and other parts of the body surface, and a distinct fall in blood pressure resulted. The fluid drawn from urticarial wheals was also tested for a histamine-like action. The results, however, were not conclusive. Only in some instances could such an action be demonstrated. The fluid was also tested upon the guinea-pig's uterus, but again little light was thrown upon this question, for, though the fluid stimulated this organ to contraction, normal plasma caused a similar effect. More recently it has been shown that extensive stimulation of the skin of a susceptible person causes increased secretion of gastric juice. This is a well-known histamine effect (p. 442).

(6) An individual upon whose skin urticarial wheals can be provoked with unusual facility by stroking (dermographism) shows a sensitivity to histamine injections that is no higher than normal. This fact indicates that the susceptibility of such an individual does not depend upon a greater responsiveness of his capillary vessels. The greater readiness with which his skin reacts to mechanical stimulation is therefore attributed to an exaggerated sensitivity of the cells of the skin to injury and a more prompt release of a diffusible substance.

The cutaneous reactions following injuries of various sorts, e.g., burning, freezing, electrical stimulation and the more slowly-developed erythema resulting from ultra-violet irradiation, are believed to be produced by the same humoral mechanism. The cardinal signs of inflammation—redness, heat, and to some extent the swelling and pain—can be similarly explained, namely, direct action of the dilator H-substance upon the minute vessels, and an indirect effect through the medium of the axon reflex, upon the arterioles of the surrounding area.

Lewis has extended this conception to embrace the cutaneous vasodilator effects of antidromic impulses discharged under ordinary circumstances from the central nervous system through the posterior roots (p. 235). The nervous impulse, it is conceived, brings about its effect upon the vessels through the release of H-substance from the cells of the epidermis, and not by a direct action upon the vascular wall.

The cutaneous lesions characteristic of herpes zoster are ascribed to the liberation of H-substance from the epidermal cells by antidromic impulses. Head and Campbell have demonstrated inflammatory changes, hemorrhages and destruction of nerve cells in the posterior root ganglia. Similar skin changes may follow involvement of the roots by malignant disease or injuries, such as the so-called trophic ulcers accompanying lesions of the sensory side of the nervous system, e.g., along the course of lightning pains in tabes. The erythema and blistering of the skin induced by the suggestion of burning or other injury during the hypnotic state may possibly be produced in a similar manner. Also it is probable that many other types of cutaneous lesions familiar to the dermatologist, e.g., vesicles, urticaria, maculae, purpuric spots, etc., have a neuro-chemical basis.

It has been suggested by Dale that acetylcholine (p. 946) probably also plays a rôle in cutaneous vascular reactions. It is not unlikely that this substance is liberated at the nerve ending on the arteriole as a result of impulses either discharged antidromically from the central nervous system or arising peripherally and reaching the vessel along the path of an axon reflex. In the latter instance the cutaneous stimulus is conceived as causing the liberation of H-substance. This excites cutaneous nerve terminals, and the impulses thereby set up being transmitted to the nerve endings on the arteriole cause the release of acetylcholine. This conception would, therefore, hold acetylcholine directly responsible for the arteriolar dilatation characteristic of the flare.

REACTIVE HYPEREMIA AND BIER'S SPOTS. If the circulation to a part is arrested for a time (as by compression with a tourniquet or a sphygmomanometer armlet) and then released, the skin flushes, the volume of the part increases and the blood flow through it is greater than before the vessels were occluded. The hyperemic reaction occurs though all nerves supplying the part have been severed, and it has been shown by Lewis and Grant that it occurs independently of any nervous influence (e.g., axon reflexes). These observers furnish evidence that it is due to the accumula-

tion of H-substance in the skin during the period of circulatory arrest. It has also been demonstrated by Barsoum and Smirk that the concentration of a substance with the biological properties of histamine increases in the venous blood of the arm after a period (10 to 30 minutes) of circulatory arrest.

During the period of circulatory arrest the skin becomes mottled, blanched areas (Bier's spots) and bright blotches appearing on the background of cyanosis. The bright areas are caused by blood delivered through the nutrient arteries of the bones and anastomatic channels to the main vessels of the limb below the obstruction. This trickle of blood forces oxygenated blood from the occluded arteries into the cutaneous capillaries. The pallid areas, which were first described by Bier in 1898, are due to capillary contraction. A new significance has been given to the latter by the observations of Rous and Gilding, who found that they occur also in the skin and other non-vital tissues of animals when the blood volume is considerably reduced. These authors look upon the localized contraction of the vessels in such instances as part of the mechanism whereby the capacity of the circulatory system is reduced and the blood supply to vital tissues thus maintained at the expense of those of less importance.

CAPILLARY PULSATION

Rhythmical changes in skin color—flushing alternating with pallor corresponding to the heart beats—may occur when the smaller arterioles of the skin become dilated. It is seen in aortic regurgitation and in arteriovenous aneurysm, and is usually ascribed to the high pulse pressure characteristic of these conditions. Lewis, however, has shown that high pulse pressure, though it enhances the phenomenon, is not a necessary condition for its appearance, for it occurs also when the pulse pressure is low. The essential factor concerned in capillary pulsation is a certain degree of dilatation of the fine arterioles beneath the papillary layer of the skin. The opening of these vessels reduces the peripheral resistance and the flow in the capillary then tends to become intermittent instead of continuous (p. 123). Pulsation in the capillaries may be demonstrated in most normal young persons, especially if peripheral vasodilatation be induced by immersing the hand in hot water, or by means of a drug such as amyl nitrite, and then observing the skin through a glass slide pressed lightly upon it. The pulsation is seen particularly well in the more highly vascularized regions, e.g., the finger tips, the cheeks, lips or ear lobes, or on the outskirts of inflamed regions. It may frequently be demonstrated in certain of these regions in normal in-

dividuals, even without preliminary dilatation, and is especially evident under the low power of the microscope. In elderly persons, however, it may be impossible of demonstration, even after the application of heat, and then it is assumed that the vessels are incapable of the necessary degree of dilatation. The capillary loops, the collecting venules and the subpapillary venous

has been measured by Landis. A fine cannula was inserted into either limb of the loop as desired and the pressure measured directly by means of the apparatus shown in fig. 120. With the hand at or above the level of the auricle (level of the manubrium sterni) the capillary pressure remains constant but increases when the hand is moved to a lower level. The increase in pressure

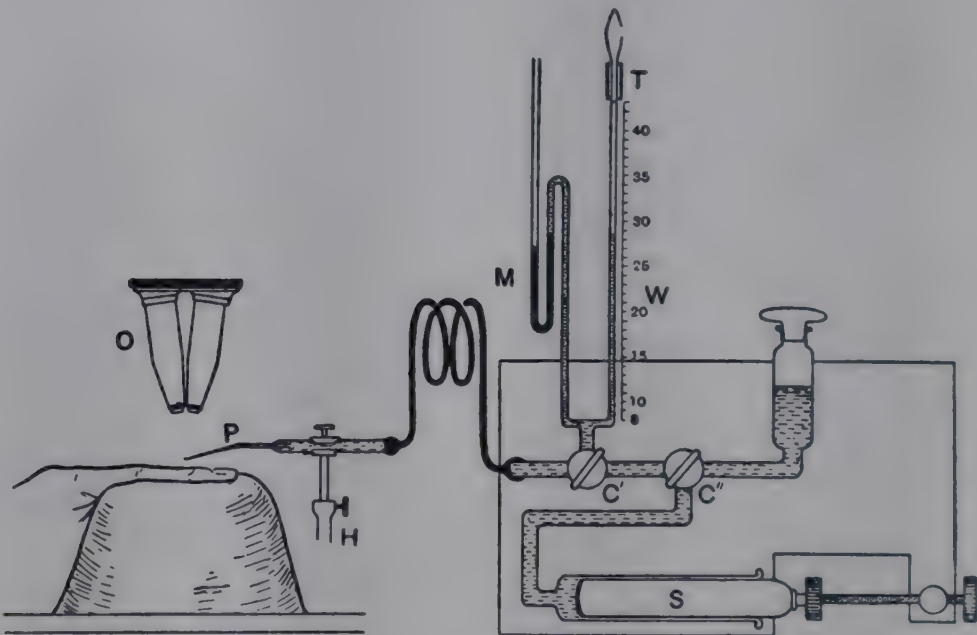


FIG. 120. Diagram of apparatus for the determination of capillary pressure by micro-injection. C', C'', three-way stopcocks; H, holder of micromanipulator; M, mercury manometer; O, binocular microscope; S, syringe. The system is filled with physiological saline to which has been added 0.3 per cent sodium citrate as an anticoagulant. When the tubing (W) is closed at T the height of the mercury column indicates the pressure exerted upon the contents of the micropipette inserted into the capillary. By means of the syringe, the pressure in the system is adjusted until the corpuscles remain in the same general position in the tip of the pipette, oscillating back and forth with each heart beat. The reading of the manometer then gives the capillary pressure. (After Landis; Heart, 1930, 15, 209.)

TABLE 22*
Gradient of pressure in the capillary loop of skin of hand

PRESSURE MEASURED IN	NUMBER OF OBSERVATIONS	CAPILLARY PRESSURE	
		Range	
		mm. Hg	mm. Hg
Arteriolar limb.....	125	21-48	32
Summit of loop.....	29	15-32	20
Venous limb.....	99	6-18	12

* Modified from Landis.

plexus, i.e., those vessels responsible for skin color, are involved in the pulsation. Capillary pulsation cannot therefore be considered as an unequivocal indication of aortic regurgitation or other pathological condition.

CAPILLARY PRESSURES

The blood pressure in the arterial and venous limbs of the capillary loops of the human finger

is in direct proportion to the distance between the new level and the base of the heart and is due to the hydrostatic pressure of the column of blood in the veins (p. 139). The average pressure in the arterial limb of the loop was found to be 32 mm. Hg, and in the venous limb 12 mm. Hg when the hand was at the level of the auricle. In the arterial limb the blood pressure was higher, in the venous limb lower, than the osmotic pressure of the plasma (see p. 42). The application of heat, venous congestion or the production of a histamine flare elevated the capillary pressures well above these values. The application of cold caused first a fall in pressure and then a small rise above the original pressure. The production of a wheal, as by freezing, resulted in a rise of the average pressure, in the arterial limb to 49 mm. Hg, and in the venous limb to 32 mm. Hg. In Raynaud's disease the pressure in the capillary loop is greatly reduced during the vascular spasm. (See Table 22.)

ARTERIO-VENOUS ANASTOMOSES

Grant and his associates have shown that in the ear of the rabbit, communications (20 to 70 micra in diameter) exist normally between the arterioles and corresponding venules (fig. 121) through which the blood may be shunted. They are also present in the human skin and in the toes of birds. At ordinary room temperature these anastomotic channels are closed, but they open when the air temperature rises or falls below a certain critical level. Local heating of the rabbit's ear does not cause dilatation until the temperature rises to between 35° and 40°C. Local cooling

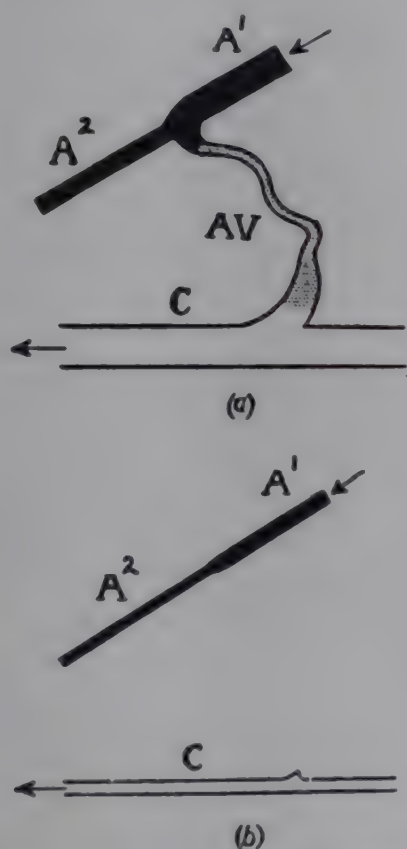


FIG. 121. Reaction of anastomosis and associated vessels to lowering of body temperature. A^1 , A^2 , artery; AV, arterio-venous anastomosis; C, vein. Upper figure (a), anastomosis open; lower figure, (b), anastomosis closed. (After Grant.)

causes dilatation which commences when the temperature is reduced to below 15°C.; above this temperature the capillaries are constricted. At 5°C. the dilatation of the anastomotic channels is general. This reaction is brought about reflexly and is not confined to the portion of the ear actually cooled, but involves the whole member and even the ear of the opposite side. In man, the blood flow in the vessels of the terminal phalanges of the fingers may increase some 100 times, as a result of the reflex dilatation of arterio-venous anastomoses. The communicating channels are believed to have two important functions; (a)

regulation of the body's temperature by increasing the radiation of heat, since when dilated they permit an enormous quantity of blood to flow through the peripheral parts. The importance of this mechanism is evident from the fact that in the rabbit the body temperature can be raised or lowered at will by heating or cooling the ears. (b) Maintenance of the temperature of outlying parts of the body against local cooling.

The arterio-venous anastomoses are supplied by constrictor sympathetic nerves, and are constricted by adrenaline. They are dilated by mechanical stimuli, by the stimulation of sensory nerves and by histamine or acetylcholine. The reactions are therefore essentially the same as those of the arterioles. In man, similar channels have been demonstrated connecting the arterioles and veins of the terminal phalanges.

THE CORONARY CIRCULATION

The heart muscle is supplied with blood from the two coronary arteries, right and left, which arise directly from the aorta close to its origin. The *right coronary* artery appears between the roots of the pulmonary artery and aorta and curving to the right in the auriculo-ventricular groove runs toward the apex in the inferior (posterior) interventricular sulcus. The part of the vessel in the auriculo-ventricular groove is referred to as the right circumflex artery and that portion in the interventricular sulcus as the posterior descending branch. Though there is considerable variation in the distribution of the two coronary vessels, in the most common arrangement (48 per cent according to Schlesinger), the greater part of the heart receives branches from the right coronary artery which supplies all of the right ventricle, the posterior half of the interventricular septum and part of the left ventricle; a special branch goes in the majority of cases to the sino-auricular node, another to the auriculo-ventricular node and bundle.

In a smaller proportion of instances (34 per cent), the distribution of each coronary vessel is largely confined to the corresponding ventricle, thus, the right ventricle and the posterior part of the interventricular septum is supplied by the right vessel while the left ventricle and the anterior part of the septum is supplied by the left. In 18 per cent of the 225 hearts examined by Schlesinger, the distribution of the *left coronary* artery predominated. It supplied the whole of the left ventricle and a variable portion of the right chamber and of the septum.

Schlesinger has analyzed his anatomical findings and correlated them with the incidence of coronary disease. His results suggest that the second group, in which the blood supply to the heart is not predominantly through either the right or the left vessel, is the least vulnerable

to arteriosclerotic changes and their effects. The group in which the distribution of the left vessel predominates, appears to be the most susceptible while that in which the right vessel supplies the greater part of the heart stands in an intermediate position with regard to the incidence of coronary disease.

The heart muscle possesses an extraordinarily rich capillary supply. In the rabbit's heart the combined capillary length per cm. of tissue is about 11 meters as compared with 6 meters for active skeletal muscle. At birth a single capillary supplies 4 or 5 cardiac fibers. During growth the muscle fibers increase in size but not in number and each fiber in the adult heart receives a capillary vessel (Wearn), the number of vessels per unit of tissue remaining unchanged from that at birth. In cardiac hypertrophy, on the contrary, the enlargement of the individual fibers is not accompanied by a corresponding increase in vascularity of the muscle. The hypertrophied heart, therefore, suffers a relative reduction in its blood supply.

ANASTOMOSES

The coronary arteries form three types of anastomoses or communications:

(1) Anastomoses between branches of one coronary with those of the other. In the normal heart, the coronary branches are essentially "end arteries" (see p. 275), that is, no pervious channels of importance exist between them.

(2) Communications with the cavities of the heart:

(a) The THEBESIAN VESSELS, described by Vieussens in 1706 and by Thebesius in 1708, are small venous channels which open into the auricular and ventricular cavities. Thebesius demonstrated the communication of these vessels with the coronary system by inserting a blow pipe into a coronary artery and blowing through it after immersing the heart in fluid; bubbles were observed issuing from the heart cavities. The relations of these channels have been studied within recent years in the human heart by Wearn and by Grant and Viko in the heart of the sheep. They have been shown to communicate on the one hand with the cavities of both ventricles, on the other with the coronary sinus and other large coronary veins, and hence with the capillary bed of the ventricular muscle.

(b) DIRECT COMMUNICATIONS BETWEEN THE CORONARY ARTERIES AND THE VENTRICULAR CAVITIES, I.E., COMMUNICATIONS OTHER THAN

THROUGH THE CAPILLARY BED. These channels have been clearly demonstrated by Wearn and his associates in human hearts and are of two types which they term *arterio-luminal* and *arterio-sinusoidal* respectively. The arterio-luminal vessels are coronary branches from 0.2 to 1.0 mm. in diameter. They run a fairly direct course and usually retain their arterial characters up to the point where they open into the lumen of the heart. The arterio-sinusoidal vessels are branches of a coronary artery which break up into a number of irregular channels varying from 50 to 250 micra in diameter. These latter are called *myocardial sinusoids*. The walls of the sinusoids are composed of a single layer of endothelial cells, run a meandering course, and anastomose very freely with one another. The arterio-sinusoidal vessels thus provide, through the myocardial sinusoids, a means of free communication between the ventricular cavities and the coronary arteries.

(3) EXTRACARDIAC ANASTOMOSES. Potential communications between auricular twigs of the coronary arteries on the one hand, and branches of the internal mammary and aorta—pericardial, bronchial, phrenic and esophageal—on the other, have been demonstrated by Hudson, Moritz and Wearn. The site of anastomosis between these two systems is in the pericardial fat, and around the openings of the great vessels. These observers injected the coronaries from the aorta with a suspension of lamp black in acacia solution. A rich network of injected vessels appeared over the entire surface of the parietal pericardium (fig. 122), over the diaphragm and in the walls of the pulmonary vessels (*vasa vasorum*). The trachea, esophagus and mediastinum also showed injected vessels. Upon injection of the aorta, after tying it off distal to the orifices of the coronaries, and at the level of the diaphragm, the injected material was found in the coronary vessels around the openings of the pulmonary veins. Pericardial adhesions increase the extracardiac anastomoses.

Beck and Tichy, in a series of experiments upon dogs, have demonstrated the feasibility of developing the extracardiac anastomoses to such an extent that they can sustain the nourishment of the heart after almost complete occlusion (85%) of both coronary vessels. Adhesions were produced by incising the myocardium and stitching the pericardium into the wound; or by removing the epicardium and the endothelium of the pericardium. In other experiments an adjacent thoracic muscle, or the omentum drawn through an incision in the diaphragm, was utilized to establish communication between the coronary vessels and an

extracardiac vascular bed. Occlusion of the coronary arteries was brought about gradually by means of silver clips which were tightened in successive operations.² An operation devised on the basis of his experimental work has been performed by Beck upon patients suffering from angina pectoris due to coronary disease; the pectoralis major muscle was employed.

O'Shaughnessy has employed an omental graft (*cardio-omental cardiopexy*) with success in the treatment of angina. The omentum possesses the power of vascularization above all other tissues. The effectiveness of such a graft was clearly demonstrated in experiments upon grayhounds. Animals with the descending branch of the left coronary ligated and an omental graft were able to race over 500 yards.

Heinbecker and Barton injected an irritant mixture into the pericordial sac of dogs. Through the adhesions

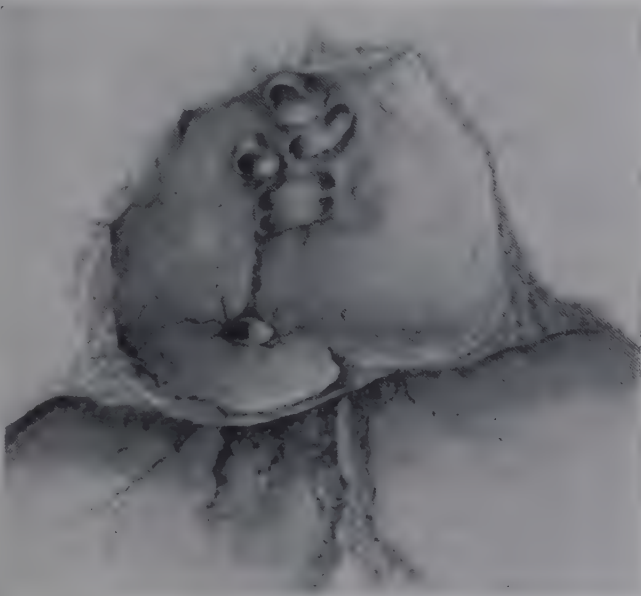


FIG. 122. Drawing of the inner surface of the parietal pericardium and the inferior surface of the diaphragm. The coronary arteries were injected and the heart removed to expose the sites of anastomoses between coronary and extracardiac vessels. (After Hudson, Moritz and Wearn.)

set up effective collateral channels are said to have been established.

Interesting and encouraging as are these various procedures designed to increase extracardiac anastomosis, their value in angina pectoris has not been proved (see Marvin).

It does not appear that anastomotic communications play any significant rôle in supplying blood to the normal heart. When a large coronary branch is suddenly occluded, the back-flow in the section of the vessel distal to the occlusion is only about 1 cc. per minute and the myocardium normally supplied by the obstructed vessel ceases to contract within from 1 to 2 minutes. Nor

²Occlusion of the coronary sinus in animals is also claimed to encourage the development of collateral channels and to reduce the mortality following ligation of a large coronary branch.

does occlusion of other coronaries reduce the back-flow in the distal section of the previously occluded vessel. On the other hand, gradual occlusion of a coronary is followed by the development of a back-flow from other coronary branches as a result of altered pressure gradients. The pressure in the peripheral section of the occluded vessel increases and may approach the aortic pressure. In the dog, the retrograde flow usually amounts to from 30–40 cc. per minute and, in some

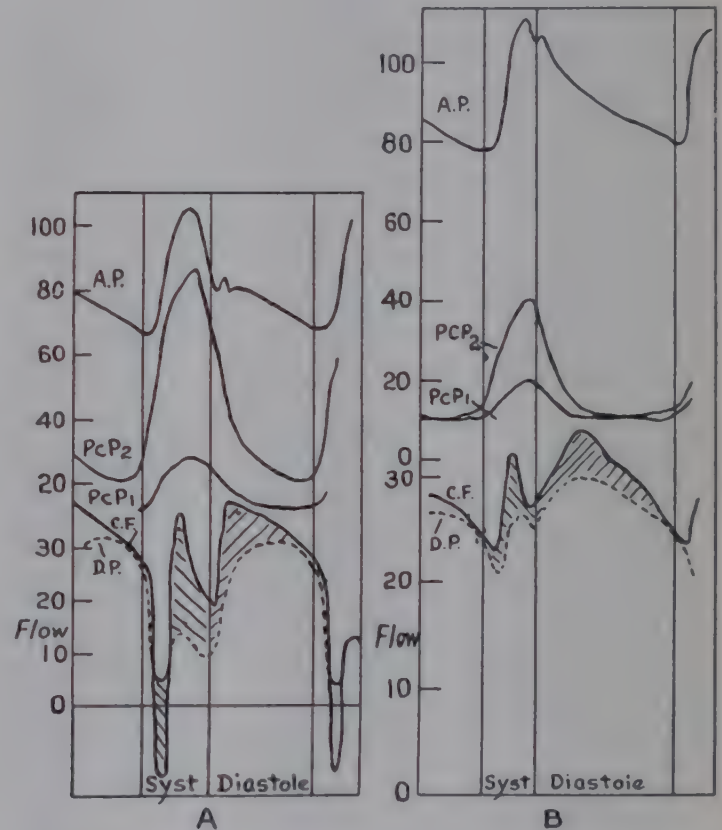


FIG. 122A. Comparison of the curves representing intramural and total inflow at a coronary orifice in the left coronary (A) and in the right coronary (B) together with the pressure curves from which the intramural flow was reconstructed. AP, aortic pressure; PCP, peripheral coronary pressure as recorded; PCP₂, peripheral coronary pressure with proper ordinate valve; CF (heavy line), inflow at a coronary orifice; DP (dashed line), differential pressure curve representing intramural flow. Shaded areas represent extramural flow. Ordinates; top, mm of mercury; bottom flow in cubic centimeters per minute. (After Gregg "Blood Heart and Circulation" p. 81 Science Press, 1940.)

instances, is over 100 cc. per minute. The myocardium, to which the occluded vessel is distributed, shows normal contractions (Gregg and associates). The importance of anastomatic channels in the supplying of the heart muscle in coronary disease is indicated by the observations of Wearn; he has reported cases in which post-mortem examination revealed the main coronary arteries to be completely occluded; yet the coronary occlusion had not been the cause of death,

but must have been of long standing. The heart muscle, apparently, had in these instances been nourished through channels communicating with the ventricles or through extra-cardiac anastomoses, or through both of these routes. According to Gross, anastomoses between the branches of the coronaries multiply with age and the vascularity of the muscle, especially of the left ventricle and septum, increases.

The possible functional significance of the communications between the coronary system and the ventricular cavity is indicated by the experiments performed some years ago by Pratt. He was able to keep the *isolated* heart of the cat beating for an hour by perfusing it through a cannula tied into the ventricle. Katz and his colleagues introduced a pure culture of killed bacteria into the superior vena cava of a heart-lung preparation (precautions having been taken that bacteria did not enter the coronary system from the arterial side). The bacteria were found later in the sinusoidal spaces, capillaries and the small arteries of the myocardium. These authors conclude that though the quantity of blood conveyed from the ventricles to the *normal* heart muscle is small, in some pathological states associated with narrowing or occlusion of coronary vessels, it may be sufficient to aid significantly in nourishing the myocardium. The results of Stella's experiments on the heart-lung preparation of the dog also indicate that in a heart whose muscle is supplied with blood through the coronary system, back-flow does not occur to any important extent from the ventricles into the coronary vessels. Even when the ventricular pressure was higher than the coronary pressure no evidence of back-flow was secured.

CORONARY CIRCULATION TIME AND VOLUME FLOW

The coronary circulation is one of the shortest in the body. The blood passes through arterioles into a capillary bed and is collected by veins which empty through the coronary sinus into the right auricle. Evans and Starling calculated that 60 per cent of the blood of the coronary circulation is delivered into the right auricle by the coronary sinus. The remaining 40 per cent must find an outlet through other channels—the Thebesian and other communications mentioned above.⁹ According to Wearn, the proportion of blood re-

turned otherwise than through the coronary sinus may, under certain conditions, be much greater than 40 per cent. The blood vessels of the left ventricle drain mainly through the coronary sinus, whereas the Thebesian vessels and other luminal vessels drain the right ventricle. A rise of pressure in the pulmonary circulation (and therefore of the pressure in the right ventricle) reduces the pressure gradient between the coronary arteries and the Thebesian vessels and causes thereby, slowing of the flow along these channels. Such slowing interferes very seriously with the nutrition of the right ventricular muscle. Moe and Visscher found that a reduction in the aortic-pulmonary pressure difference to 40 mm. Hg, either by a fall in aortic pressure or a rise in pulmonary pressure, diminished the Thebesian flow to 20 per cent of the normal. The dependence of the nutrition of the right ventricle upon the venous return through the Thebesian vessels is probably the reason that this side of the heart can work for a relatively short time against a high pulmonary resistance (e.g. mitral stenosis or pulmonary fibrosis) whereas the left ventricle is able to work for years against a high aortic pressure, since the flow from the coronary sinus is not affected by the high pressure in the left ventricle. A rise in aortic pressure by increasing the pressure gradient might therefore be expected to benefit cases of cardiac disease with raised pulmonary pressure. Such benefit has been observed.

The coronary circulation time, that is, the time taken for a red cell (following the shortest route) to pass through the coronary system is about 8 seconds as compared with 20 seconds through the vessels of the limbs.

Experiments upon animals (heart-lung preparation) indicate that about 5 per cent of the total output of the heart flows through the coronary system. The output of the human heart under basal conditions is between 3 and 4.6 liters per minute, but during strenuous muscular exercise it may, in the case of a large muscular subject, rise to 37 liters. In such an instance, if the volume of the coronary flow were 5 per cent of the total blood flow, nearly two liters would pass through the coronary system. The coronary flow in man can be estimated in another way. The work of the heart, for example, can be calculated approximately from the cardiac output and the mean arterial blood pressure (p. 115). Taking the efficiency of the heart at 20 per cent, the oxygen consumed by the myocardium can

⁹The latter is probably only a very approximate figure which varies considerably under different conditions, such as, especially, the pressure in the right ventricle.

be calculated from the work performed. The results of such calculations indicate that the heart muscle during strenuous exertion consumes as much oxygen as does the entire body during rest (Hill), or about 250 cc. per minute. Assuming that during maximum muscular effort the coefficient of oxygen utilization is 0.7 (p. 322), that is to say, the heart muscle removes about 13 cc. of oxygen from each 100 cc. of blood, (arterio-venous oxygen difference = 13 vols.) then the delivery of 250 cc. of oxygen requires a flow of $\left(\frac{250}{13} \times 100 = \right)$ about 2 liters of blood through the coronary system per minute, or an amount of blood having a weight more than 6 times greater than that of the heart itself (300 gm.). The coefficient of oxygen utilization of the heart muscle is probably, in most instances, lower than the figure given; the blood flow would then be greater for an equivalent oxygen consumption. The A-V oxygen difference of the coronary blood of the dog at rest is from 8 to 16 volumes.

THE CORONARY FLOW DURING DIFFERENT PHASES OF THE CARDIAC CYCLE

Scaramucci, an Italian of the 17th century, was the first to recognize that unlike other arteries the flow through the coronary arteries occurred mainly during diastole, and that a reduced amount of blood entered the vessels during systole owing to their compression by the contracting cardiac muscle. Stroem offered an anatomical reason for the reduced flow during systole, namely, that the leaves of the aortic valves blocked the coronary orifices during this phase of the cycle. This explanation was soon shown to be incorrect, for the edges of the open valves in many cases do not reach as far as the coronary orifices. Langendorff studied the problem intensively in the perfused isolated heart, and our knowledge of the coronary flow during the cardiac cycle is based largely upon his work. In more recent times, Anrep and his colleagues in England, and Wiggers, Green and Gregg with their associates in America have been the outstanding contributors in this field.

The coronary inflow. The flow in the coronary system is affected profoundly by the compressing force of the cardiac muscle during systole. The flow through the peripheral vessels, which are surrounded by muscle and are directly compressed, is referred to as the *intramural flow*. The flow through the larger more superficial coronary

branches, is called the *extramural flow*; and is affected both directly and indirectly by compression during systole. The total flow (intra and extramural) in a coronary vessel can be determined by perfusing the vessel through its orifice and measuring, by some form of flow meter, the quantity of fluid which enters. But such a method has the disadvantage that the coronary circulation is not maintained under natural conditions, that is, with a normal pulsatile aortic pressure. Wiggers and his associates find, however, that the pressure in the peripheral coronary vessels never rises as high as the aortic pressure, that is, the pressure gradient is not abolished at any time during the cardiac cycle. The intramural flow, therefore, is not completely arrested. But, two sharp reductions in the flow occur, one in the isometric period and at the beginning of ejection, the other in the latter part of the ejection period. The rate of flow is greatest in mid-systole and throughout diastole.

The curve of total coronary flow (intra and extramural) as measured at a coronary orifice, resembles that of the intramural flow, except that the total flow is *completely* arrested during early systole and is greater during mid-systole and the first half of diastole. The arrest of the total orifice flow in early systole is attributed to compression of the deeply placed vessels which forces blood backwards into the larger superficial vessels and thus opposes the flow from the aorta at this time. But the pressure in the peripheral vessels never rises as high as the aortic pressure, so that the onward flow in these vessels is never completely stopped. As the aortic pressure rises during systole, the superficial vessels are distended and the extramural flow increases over that in the deeper-lying and compressed intramural vessels. During early diastole, the peripheral vessels are quickly released from compression and the flow through the extramural vessels, no longer impeded by back-flow, is augmented.

The contours of the blood flow curves of the *right coronary* differ from those of the left vessel in that the reduction in the rate of flow in early systole is not nearly so pronounced and the rate of total orifice flow does not exceed the intramural flow to as great a degree (fig. 122A). The flow during systole may approach or even exceed that during diastole.

The thermo-stromuhr of Rein (p. 145), as modified by Baldes and Herrick, has been employed by Essex

and associates for measuring the coronary flow in conscious animals (dogs). The chest was opened and the instrument placed in position. The connecting wires were then led to the exterior and the chest closed. After recovery from the operation, blood flow determinations were made from time to time under various physiological conditions. The flow was found to be increased during digestion by over 80 per cent and by about 400 per cent when the animal performed strenuous work.

Coronary Pressures

The pressure curve of a coronary artery has a form closely resembling the aortic pressure curve. The minor differences which are to be seen in the pressure pulse of a coronary artery are not peculiar

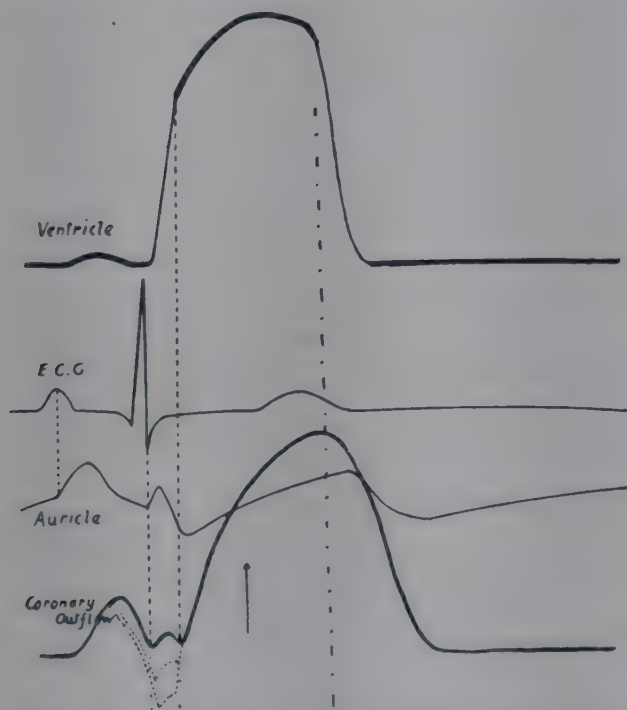


FIG. 123. The relation of coronary outflow to other events in the cardiac cycle. (After Anrep and associates.)

to that vessel but appear in pulses recorded from other branches of the aorta. The pressure in the right coronary artery is lower than in the left coronary but is considerably higher than the pressure in the right ventricle, whereas the pressure in the left coronary is lower than the left ventricular pressure. The pressure in the coronary sinus amounts to 10 or 12 mm. Hg.

The outflow from the coronary sinus. The flow from the coronary sinus is increased slightly during the latter half of auricular systole and very greatly during ventricular ejection. A graphic record of the outflow, therefore, shows two well-defined waves (cf. fig. 123). The first and smaller wave is probably due to the compression of the walls of the coronary sinus by the auricular muscle and the expulsion of a small quantity of blood. Evidence for the dependence of this wave upon

auricular contraction is, that it occurs during the latter part of the P deflection of the electrocardiogram, that it disappears during auricular fibrillation, and that in heart block it synchronizes with the auricular contractions.

The large wave occurring during the ejection phase of ventricular systole is due to the blood being squeezed from the coronary veins by the grip of the ventricular muscle. At the end of ventricular systole the outflow falls suddenly as a result of the release of the veins from the compressing force of the muscle. The vessels having been practically emptied must refill before the flow from the coronary sinus is resumed.

A diminutive wave is seen in the figure between the two waves just described. It occurs during the isometric period of ventricular systole but its cause is uncertain.

FACTORS REGULATING THE CORONARY CIRCULATION

(1) *THE AORTIC BLOOD PRESSURE.* The height of the mean aortic pressure, and especially of the mean pressure in the aorta following the closure of the semilunar valves (postdiastolic pressure), and the resistance in the peripheral coronary vessels are the most important factors determining the coronary inflow. For example, in aortic regurgitation, or arterio-venous aneurysm produced experimentally, the coronary flow is decreased due to the sharp fall in diastolic pressure, but in these conditions during systole, the aortic pressure is elevated to a greater degree than the peripheral coronary pressure. The steeper pressure gradient results in a greater systolic flow which compensates, in part, for the decreased flow during diastole. In experimental aortic stenosis systole is prolonged and the coronary flow correspondingly reduced; the flow during diastole is not significantly affected.

(2) *INNERVATION OF THE CORONARIES.* Woolard has demonstrated by histological studies that the coronary vessels are richly supplied with both vagal and sympathetic fibers. The larger branches were found to be innervated about equally by the two types of nerve, whereas the arteriolar innervation was mainly through the vagus. The action which each of these two sets of fiber exerts upon the heart has, however, been a moot question for several years and a very difficult one for investigation, since stimulation of the vagus, or of the sympathetic, causes changes in the action of the heart which in turn influence the coronary circulation.

Though the question of the actions of the vagus and sympathetic nerves upon the coronaries has not received a final answer, the weight of evidence indicates that, in the mammal, the vagus is vasoconstrictor, while the sympathetic and adrenaline are vasodilator. Anrep and Stacey observed an increase in coronary flow of 85 per cent after the administration of adrenaline, and several workers have reported an increased flow from stimulation of the stellate ganglia. Mann and associates, employing the thermo-stromuhr, observed an increase of 300 per cent in the coronary flow after the administration of adrenaline or ephedrine. Wiggers showed that stimulation of the peripheral end of the cut vagus in an animal under the influence of atropine, which in suitable dosage abolishes the vagal action upon the heart but not upon the coronaries, reduced the flow from a coronary vein. Diminution in coronary flow upon vagal stimulation was also demonstrated by Anrep and Segall, using the heart-lung preparation and the hot wire method of recording. The effect persisted though constancy of heart rate was secured by atropinization. Anrep and Segall also found that the coronary flow was increased considerably after vagal section, a fact which indicates that these nerves exert a tonic vasoconstrictor influence. The vagus, as we know, exerts its effect through the liberation of acetylcholine, and this substance has been demonstrated by Feldberg and Kraye in the coronary blood during vagal stimulation. One would therefore expect acetylcholine to reduce the coronary blood flow. On the contrary, this chemical dilates the coronaries in mammals, an effect which is not abolished by atropine; it has a pronounced constrictor action, however, upon the coronaries of birds (see also Gregg).

The coronary dilatation and consequent increase in flow which follow sympathetic stimulation or adrenaline administration are what one should be led to expect from the known emergency function of the sympatho-adrenal mechanism. Through the action of this mechanism the efficiency of the body in the performance of work or in combating the dangers of the environment is raised to a high level; the mean arterial blood pressure is elevated as a result of vasoconstriction in the skin and splanchnic areas while the vessels of the contracting skeletal muscles and brain are dilated; the force of the cardiac contraction is augmented. It would be odd if such effects, directed toward the general improvement of the circulation during muscular effort, were antago-

nized by a coincident constriction of the coronary arteries. But perhaps the question of the sympathetic action upon the coronaries is really of no great practical importance since the response of the coronaries in dogs after sympathetic denervation is just as great as in normal animals; nor is the dilator effect following stimulation of the stellate ganglion pronounced. The coronary vessels are also supplied with afferent fibers from both the vagus and the sympathetic. Coronary reflexes initiated from the abdominal and thoracic viscera have been demonstrated. Thus, stimulation of the abdominal organs in animals has been shown to cause coronary constriction. A coronary dilator reflex is initiated by a rise of pressure in the right auricle or vena cava.

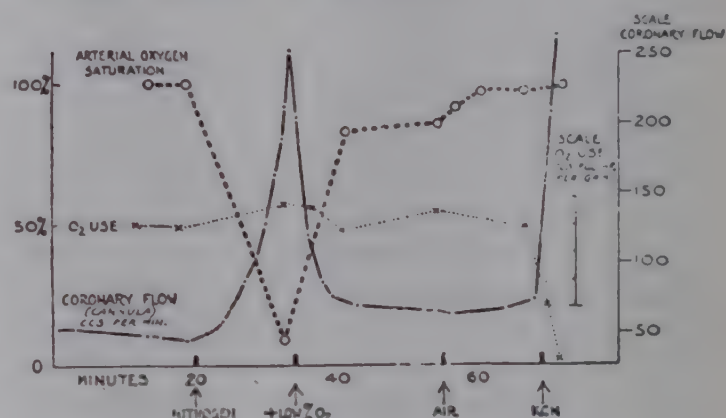


FIG. 124. Curves showing the relation of the coronary blood flow and of the oxygen consumption by the heart to the oxygen saturation of the blood passing through the coronary vessels. (Hilton and Eichholtz.)

(3) ALTERATIONS IN THE OUTPUT OF THE HEART.

Increase in the venous inflow, and so in the minute volume of the heart, the mean aortic pressure being kept constant, markedly augments the flow through the coronary system if the vagus nerves are intact. On the contrary, a rise in the cardiac output with a constant aortic pressure, exerts a negligible influence upon the coronary circulation after the vagus nerves have been cut. The calibers of the coronary vessels are evidently widened as a result of a reflex inhibition of the constrictor tone of the vagus. This response, which is known as the *coronary reflex*, is not abolished by excision of the stellate ganglia.

(4) OXYGEN LACK AND CARBON DIOXIDE EXCESS. Anoxia increases the coronary flow very greatly. Reduction in the oxygen saturation of the arterial blood below 20 per cent was shown by Hilton and Eichholtz to cause maximal dilatation of the coronary vessels and a five-fold increase in flow (fig. 124). The addition of cyanide to the coronary blood exerted a similar effect. Carbon dioxide and lactic acid in the absence of a

reduced oxygen supply caused only a very moderate dilatation of the coronary vessels. Reactive hyperemia (p. 271) is a very pronounced phenomenon of the coronary circulation (Katz and Lindner).

(5) **VARIATIONS IN HEART RATE.** It is to be expected that, since the coronary arteries fill during diastole and are compressed during systole, an increase in heart rate, which causes shortening of diastole relatively to systole, will decrease the coronary flow. A diminution in coronary flow does occur when the rate of beating is so great that the total time occupied each minute by the diastolic periods (minute-diastole) is much reduced. When the rate is very slow, other factors remaining constant, the flow is augmented. Within the physiological range, however, a change in heart rate (70 to 180) appears, in itself, to have little effect upon the coronary flow.

(6) **DRUGS.** Nitrites, cyanides, caffeine, camphor, adenosine and mecholyl increase the coronary flow. The action of histamine varies in different species; the drug exerting a constrictor action upon the coronaries in the rabbit but a dilator effect upon those of the cat. By means of the thermostromuhr Essex and his colleagues have investigated the action of a number of drugs on the coronary flow in unanesthetized dogs. Histamine, coramine (pyridine- β -carboxydiethylamide), atropine and nembutal were found to increase the flow from 60 to 100 per cent; pituitrin decreased it by as much as 80 per cent. Thyroxine increased the flow by 250 per cent. The effects of adrenaline and acetylcholine upon the coronary blood flow have been mentioned. Alcohol, according to Sulzer, when it reaches a concentration in the blood of 0.1 per cent or more causes constriction of the coronary vessels and a reduction of the coronary flow. Drugs which increase the coronary flow in normal hearts have apparently little or no effect in increasing the blood supply to an infarcted area.

DISEASE OF THE CORONARY ARTERIES

The coronary arteries are very frequently the site of degenerative changes—atheroma and sclerosis—especially after the fifth decade of life. These changes, when advanced, lead to narrowing of the arterial lumina and a gradual insufficiency of the blood supply to the heart muscle. Milder grades of coronary disease are usually unaccompanied by symptoms or any clinical signs. Two conditions, namely, *angina pectoris* and *acute coronary occlusion*, are commonly associated with the more severe grades of coronary sclerosis. Auriculo-ventricular, or bundle branch block, *pulsus alternans* (Chapter XXIV) and low voltage electrocardiograms are other consequences of coronary disease.

Angina pectoris—angina of effort

These terms are given to paroxysms of severe and often agonizing cardiac pain which occur usually as a result of exertion, and last for a few seconds or minutes. The pain is felt most usually beneath the upper or middle third of the sternum; it is frequently referred to the neck, left shoulder or arm. During the attack, electrocardiographic changes frequently appear similar to those seen in coronary thrombosis (p. 281).

Anginal attacks are most commonly precipitated by effort or some form of emotional excitement, under which circumstances the minute volume of the heart is increased but the blood supply to the myocardium is inadequate for the extra work demanded of it. An increase in the cardiac output has been demonstrated in anginal attacks. The increased work of the heart during digestion also in all likelihood accounts for the common occurrence of angina following a heavy meal. Effort at this time is particularly likely to precipitate an attack in a susceptible subject.

Several views have been expressed concerning the cause of anginal pain, e.g., spasm of the cardiac muscle, sudden stretching of the wall of the aortic arch or contraction of the coronary arteries. There is, however, no change in the rhythm of the heart which would indicate the existence of spasm; distension of the aorta in animals by means of a dilator introduced through the carotid does not give rise to pain, and since the coronary vessels are so often hard and stiff spasmodic constriction of their lumina seems out of the question. The pain is evidently directly related to anoxia of the heart muscle—the oxygen supply being inadequate for the work which the heart is called upon to do.

Angina, for example, may occur though the coronary vessels are normal if the oxygen supply to the tissues is deficient, as in anemia or in rarefied atmospheres; and in aortic regurgitation the coronary circulation may be so diminished as a result of the low diastolic pressure (p. 278) that anginal attacks occur though the heart vessels themselves are fairly healthy. Also in hyperthyroidism, when the burden thrown upon the heart is already greatly in excess of the normal, the extra cardiac work occasioned by exertion may so tax a normal coronary system to furnish an adequate blood supply to the heart muscle, that cardiac pain results. In severe anemia, the low oxygen-carrying capacity of the blood is compensated during rest by an increase in the circulation

rate; the coronary flow is then adequate, the heart is able to perform the extra work entailed and the tissues do not suffer from oxygen lack (p. 356). Upon exertion, however, the heart is called upon to increase its output further in order to furnish the required amount of oxygen to the contracting muscles. But the urgent demands of the heart muscle itself for extra oxygen cannot be met, since the coronary flow is already near its maximum—anoxia of the myocardium and of the tissues in general results. In cardiac hypertrophy and dilatation, anginal attacks may also occur, though the coronaries are not diseased, and is then apparently the result of the small coronary flow *relatively* to the size of the heart (p. 274). When congestive failure supervenes the greater oxygen requirement of the inefficient myocardium (p. 218) is an additional factor.

Additional support for the view that anoxia is the prime factor in precipitating an anginal seizure is afforded by the observations of Katz and his colleagues. General anoxia induced in subjects of the disease by having them breathe an oxygen-poor atmosphere was accompanied by the appearance of characteristic electrocardiographic features (reduced amplitude or inversion of the T wave and depression of the S-T segment); a third of the subjects experienced typical anginal pain. Anoxia produced in the same way in normal subjects caused similar features to appear in the electrocardiogram, though pain was not experienced.

The pain of angina pectoris is believed to be produced in a manner essentially the same as that in which the pain of intermittent claudication is produced, namely, through the stimulation of afferent nerve endings in the myocardium by metabolic products accumulated as a result of oxygen deficiency (p. 257).

The anginal attack is treated by means of nitrites (amyl nitrite, nitroglycerine, sodium nitrite) which by causing peripheral vasodilatation reduce the work of the heart and through their dilator effect upon the coronary vessels tend to increase the blood supply to the cardiac muscle. Amyl nitrite which is administered by inhalation acts almost instantaneously but its action is evanescent; it is therefore employed to arrest an attack. The other nitrites act more slowly but their effects are more lasting; they are used in the intervals between attacks. Adenosine compounds (p. 253) are also sometimes employed for their vasodilator effects. Complete thyroidectomy, which by lowering the metabolic rate reduces the cardiac work, has been advocated in certain selected cases (p. 226).

The impulses giving rise to cardiac pain pass from the heart to the central nervous system mainly via the inferior cardiac nerve, the upper four or five thoracic ganglia and the corresponding white rami and posterior nerve roots (see referred pain, p. 514). Pain is not, apparently, transmitted through the vagus. Sutton and Lueth found that in conscious dogs, traction upon a ligature passed loosely around a coronary artery and brought out through the thoracic wall was followed by nausea, vomiting and evidence of pain. The response was abolished after removal of the stellate ganglia but persisted after section of the vagi.

Removal of the left stellate ganglion or the injection of alcohol around the upper five left thoracic ganglia (paravertebral injection) is sometimes resorted to for the relief of anginal pain. The afferent nervous pathways are thus interrupted and the patient is relieved of his attacks. No change in the underlying condition responsible for the pain is brought about by these measures, and since pain is a signal which warns the patient against heart strain, its abolition is not an unmixed blessing.

Acute coronary occlusion. Coronary thrombosis. Cardiac infarction

Smith in 1918 studied the effects of ligation of various branches of the coronary vessels in dogs. Of 11 animals in which the anterior descending branch of the left coronary was ligated 10 survived. The left circumflex artery was ligated in 14 animals; 6 survived. Ligation of the right coronary close to its origin was performed in 8 animals, only one of which recovered from the operation. In 18 animals the anterior descending branch of the left coronary and one or more branches of the left circumflex artery were tied; only 4 animals recovered from this operation; 9 died within 24 hours, 3 others died from infection and 2 from failing heart on the 15th and 17th days respectively.

Clinically, thrombosis is the commonest cause of acute coronary occlusion, though occasionally a vessel is blocked by an embolus. Obstruction of a main branch of a coronary artery is accompanied usually by severe pain, similar in character to that described under angina pectoris; dyspnea; nausea and vomiting; and often the signs of profound collapse. Other features of the attack are low blood pressure, fever, and leucocytosis. A fatal termination (due probably in many instances to ventricular fibrillation) either during

the attack or a short time later is common. The nausea and vomiting together with the fact that the attack not infrequently followed a heavy meal or a drinking bout has led in the past to many cases of coronary thrombosis being diagnosed as "acute indigestion." The underlying cause of coronary thrombosis is usually atheroma or

supplied by the occluded vessel softens, undergoes necrosis and is finally replaced by a scar; or the heart may rupture through the infarcted area, death then resulting from hemorrhage. Cardiac hypertrophy may be a delayed effect of coronary occlusion (p. 220). Minor coronary branches may become obstructed without giving rise to any

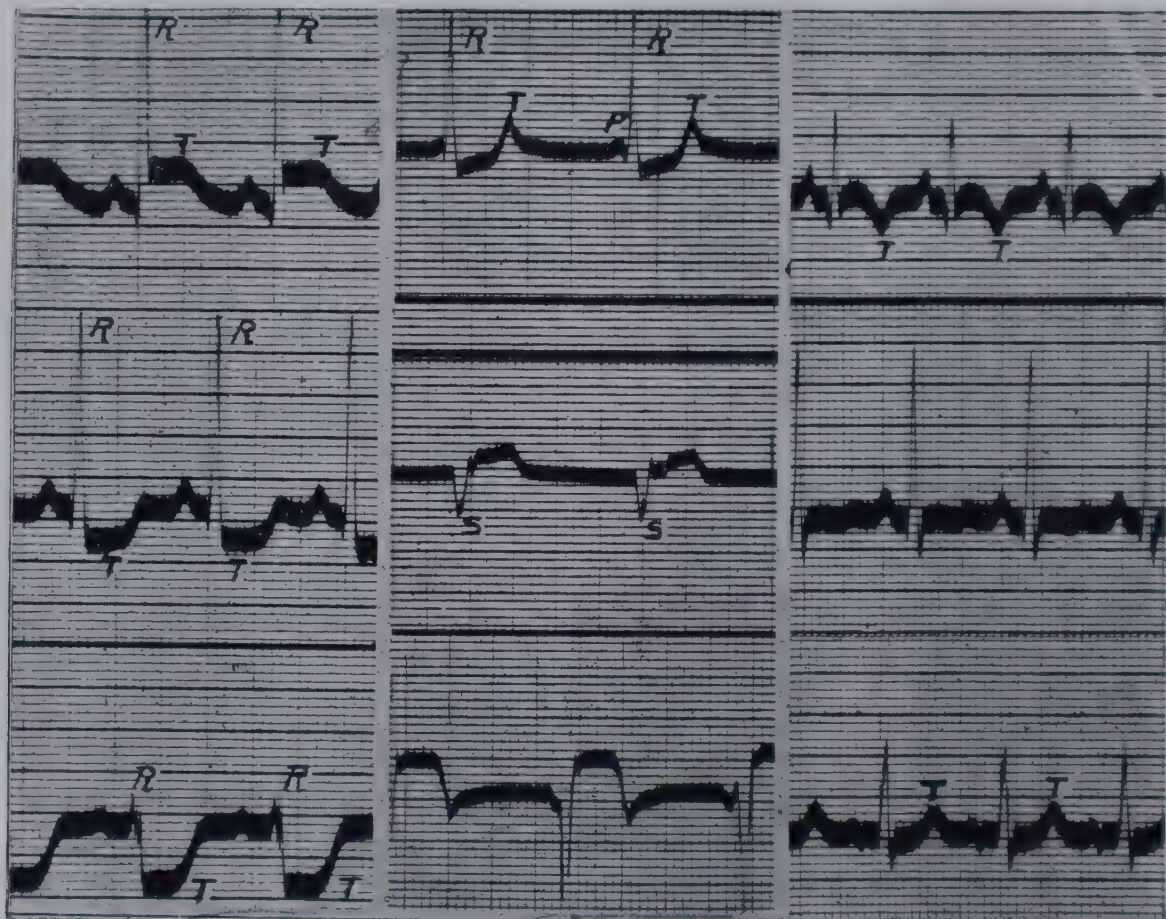


FIG. 125. Electrocardiogram in acute coronary occlusion. *a*, T_1 , type of tracing; *b*, T_2 , type; *c*, same patient as (*a*) 16 days later. (Kindness of Dr. John Hepburn.)

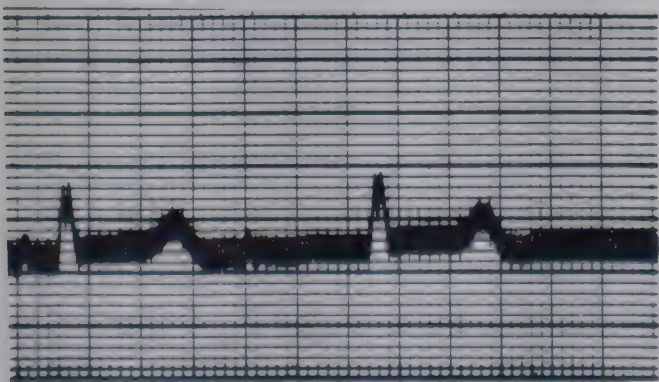


FIG. 126. Low voltage electrocardiogram, lead III. (Kindness of Dr. John Hepburn.)

sclerosis of the arterial wall and a gradual constriction of its lumen. The majority of subjects have suffered previously from anginal attacks. The anterior descending branch of the left coronary is most frequently thrombosed and for this reason has been called the *artery of sudden death*.

If death does not result from the immediate effects of the attack the area of myocardium

symptoms, the myocardial area involved being nourished through collateral vessels; or, should the occlusion of even a large branch occur gradually, collateral channels become established which are sufficient to maintain the vitality of the area of distribution of the obliterated vessel (p. 274).

The electrocardiogram immediately following an attack of coronary thrombosis often shows characteristic features which were first pointed out by Pardee. Similar features were described by Smith following coronary ligation in dogs. In occlusion of the anterior descending branch of the left coronary, the most usual electrocardiographic changes are as follows. The descending limb of the R deflection in lead I does not reach the base line but gives rise in its lower third to the T wave, i.e., the R-T interval lies well above the base line (see fig. 125*a*). In lead III, on the other hand, the descending limb of R passes below the base line but does not rise sharply again before

giving rise to the T wave; the S-T interval is therefore depressed. In occlusion of the right coronary it is usual to find these characteristic features in the two leads reversed, the S-T interval being depressed in lead I and the R-T interval elevated in lead III (fig. 125*b*). The electrocardiogram changes in character as recovery progresses, gradually returning to normal though an inverted T wave in lead I (left coronary occlusion) or in lead III (right coronary occlusion) often persists. The electrocardiogram resulting from left coronary occlusion is therefore frequently referred to as the T_1 type of record (fig. 125*c*); that associated with occlusion of the right artery as the T_3 type. (Parkinson and Bedford)

Probably the most characteristic electrocardiographic feature of coronary occlusion is the variability of the tracing from day to day during the period following the attack.

LOW VOLTAGE ELECTROCARDIOGRAMS. These are seen most frequently in subjects of myocardial degeneration resulting from coronary disease (fig. 126). The range of voltages for the normal electrocardiogram is given on page 181. Low voltages are also seen in a certain proportion of cases of hypothyroidism and in massive pericardial effusions. Electrocardiograms showing these low voltages, except in the last two mentioned instances, are of grave prognostic significance. In 68 per cent of a series of cases observed by Hepburn and Jamieson the average duration of life after this electrocardiographic feature had been first observed was 6 months.

THE PULMONARY (LESSER) CIRCULATION⁴

The blood is conveyed from the right to the left side of the heart through the pulmonary circuit, and the quantity passing per minute obviously must equal the quantity flowing in the same time through the rest of the body, namely, from 3 to 4.6 liters under basal conditions. The pulmonary vessels like those of the systemic system consist of arteries, arterioles, capillaries and veins; the pulmonary arteries break up abruptly into short, wide branches. The minute vessels of the lung, unlike those of any other vascular area, are almost surrounded by air. Though each capillary is only from half to one millimeter in length and of the order of 10 microns in diameter, the total capillary surface exposed to the lung air has been estimated at about 140 square meters (Hufner).

The vessels of the lung are highly distensible and their capacity alters with (a) changes in intra-thoracic pressure incident to the respiratory movements, and (b) alterations in the minute volume of the right ventricle in relation to the resistance on the left side of the heart.

The velocity of flow through the individual pulmonary vessels varies directly with the output of the right ventricle and inversely with the capacity of the vascular bed. That is, the capacity of the vessels remaining constant, an increase in the output of the right ventricle increases the velocity of flow in the minute vessels (p. 148) and vice versa. An increase or decrease in the capacity of the vessels and thus in the total sectional area of the vascular bed, the right ventricular output remaining unchanged, slows or quickens, respectively, the blood flow through the pulmonary circuit.

The mean arterial pressure in the pulmonary circuit has a value approximately a sixth of that in the aorta—about 25 mm. Hg in the dog and probably from 18 to 20 mm. in man. A systolic pressure of around 40 mm. Hg and a diastolic pressure of about 10 mm. Hg have been recorded in the dog, i.e., a rise in pressure of 30 mm. Hg occurs with each heart beat. In contrast to the systemic circulation the pulmonary circuit has, therefore, a pulse pressure of higher value than the mean pressure. In the dog, the velocity of flow in the pulmonary artery is around 0.4 meters per second. The pressure in the pulmonary veins is ordinarily near the zero level—from -3 mm. H_2O in inspiration, to +4 mm. H_2O during expiration. The tone of the pulmonary arterioles is relatively low, so that a rise in the pulmonary venous pressure is readily transmitted to the arterial side. As a result of the high degree of distensibility of the pulmonary vascular bed, due mainly to the opening up of fresh capillaries, the blood contained within the lungs shows wide variations under different conditions. Unless extreme, variations in the quantity of blood in the lungs are accompanied by little or no change in pressure. Ordinarily the lungs hold about 9 per cent of the total blood volume during inspiration and 6 per cent during expiration; under certain circumstances the quantity of blood in the pulmonary vessels may increase to 20 per cent or more of the total blood volume. Increased resistance to the flow of blood in the pulmonary veins, as in mitral stenosis or as a result of failure of the left ventricle (p. 222), raises the pressure in the pulmonary system. Engorgement of the

⁴The bronchi and bronchial lymph nodes, the interstitial tissue of the lungs and the walls of the larger arteries are supplied by systemic vessels, small branches of the aorta p. 294.

lung vessels results, the distended capillaries encroach upon the air spaces and the vital capacity, in consequence, is reduced. Also, increased filling of the right heart during muscular exercise results in a greater systolic discharge from the right ventricle into the pulmonary circuit. The left ventricle does not respond instantly to the greater inflow, but only after a beat or two, or until the pulmonary venous pressure rises sufficiently to distend the ventricular cavity and stretch the muscle fibers (p. 216). The ventricle then discharges as much blood as it receives. The rise in venous pressure has, however, resulted in distension of the pulmonary vessels and an increase in the total quantity of blood contained in the lungs. This ready distensibility of the vascular bed of the lungs accounts for the fact that little or no rise in pulmonary arterial pressure occurs during muscular exercise, despite the great increase in cardiac output. Nor is the pulmonary blood pressure elevated in experimental renal hypertension.

The blood flow from the venae cavae into the heart remaining constant, a rise in aortic pressure is attended by a rise in pulmonary arterial pressure. This is not a "back-pressure" effect due to the left ventricle failing to discharge its contents adequately against the raised systemic resistance, but is the result, as shown by Anrep and Bulatao, of the greater quantity of blood returned to the right ventricle through the coronary system and, in consequence, of the larger quantity discharged into the pulmonary circuit.

THE EFFECTS OF THE RESPIRATIONS UPON THE PULMONARY AND SYSTEMIC BLOOD PRESSURES

The pulmonary arterial pressure falls during ordinary inspiration and rises during expiration. One should expect that, as a result of the increased flow of blood into the right ventricle during inspiration, and the greater systolic discharge, the pulmonary pressure would *rise* during this phase of respiration. Due, however, to the traction exerted upon the circumference of the pulmonary vessels by the surrounding lung tissue, their capacity is increased. This more than compensates for the greater amount of blood entering the pulmonary circuit during the inspiratory phase. During expiration these effects are reversed. The right systolic discharge is less but the capacity of the vascular bed of the lungs is at the same time reduced; an upward swing in pulmonary arterial pressure occurs. With

maximal expansion of the lungs or during a forced expiration with the glottis closed (Valsalva's experiment, p. 138) the vessels are strongly compressed by the surrounding lung tissue and the pulmonary arterial pressure rises sharply.

The increased capacity of the pulmonary vessels during inspiration reduces, momentarily, the flow of blood into the left auricle; the consequent reduction in the systolic discharge of the left ventricle causes a fall in aortic pressure. After a few beats of the right ventricle the greater capacity of the pulmonary vessels again becomes filled and the flow of blood into the left chambers of the heart increases; the aortic pressure rises. The succeeding expiration by reducing the capacity of the pulmonary vessels drives blood to the left side and further increases the discharge into the



FIG. 127. Curve of arterial blood pressure, showing the effect upon it of the respirations. For the sake of simplicity the smaller waves due to the heart beat, and normally seen superimposed upon the respiratory waves, have been omitted.

aorta; the systemic pressure, in consequence, continues its rise until near the end of the expiratory phase. The large undulations which appear in the blood pressure tracings of animals are due to these effects. If the respiratory movements and the systemic blood pressure are recorded simultaneously it is found that the blood pressure commences to fall at the commencement of inspiration and reaches its lowest point in the latter half of this phase, the blood pressure tracing then commences to rise and reaches its maximum toward the latter part of expiration⁵ (fig. 127).

NERVOUS REGULATION OF THE PULMONARY VESSELS

The pulmonary vessels receive vasoconstrictor fibers through the *sympathetic*. The first definite evidence of a vasoconstrictor supply to the vessels of the lung was secured by Bradford and Dean who stimulated the peripheral ends of the thoracic nerves from T2 to T7 in the dog and observed a rise in pulmonary arterial pressure without any

⁵ See Heinbecker.

change in heart rate or in systemic blood pressure. Daly and Euler have obtained evidence that the sympathetic of the dog also contains vasodilator fibers. Adrenaline causes constriction of the pulmonary vessels, except in high dilution when it causes vasodilatation.

The *vagus* of the dog carries both vasoconstrictor and vasodilator impulses to the lung. The distribution of the vasoconstrictor and vasodilator fibers to the pulmonary vessels varies considerably, however, in different species. Though in the dog, as just stated, both the sympathetic and the *vagus* contain vasoconstrictor as well as vasodilator fibers, sympathetic stimulation gives predominantly vasoconstrictor⁶ and vagal excitation vasodilator effects. In the rabbit, on the other hand, only constriction of the pulmonary vessels can be obtained by stimulation of the *vagus*; this effect is abolished by atropine and enhanced by eserine. Further evidence of the vasodilator action of pulmonary parasympathetic fibers in the dog and of their vasoconstrictor action in the rabbit is provided by the action of acetylcholine; this parasympatho-mimetic drug causes dilatation of the pulmonary vessels of the dog, and constriction of those of the rabbit.

It is probable that the innervation of the pulmonary vessels is of little physiological importance. Indeed, the need of vasomotor control of the pulmonary circulation is not evident.

PULMONARY CARDIOVASCULAR REFLEXES

Evidence for the existence of proprioceptors in the vascular bed of the lungs has been furnished by the experiments of Schwegk and of Daly and associates. The latter perfused the pulmonary and the systemic vessels separately with oxygenated blood. Increased pressure in the pulmonary circuit caused a slight fall in systemic arterial pressure and an increase or a decrease in the heart rate. The fall in systemic blood pressure was more readily produced by raising the pressure in the pulmonary veins, as may follow obstructing the outflow from the left auricle. The effect is evidently purely reflex in character, for it is abolished by section of the vagosympathetic nerves. A reflex of this character may play some part in the fall of

⁶One is tempted to doubt that these experimental results reflect what actually occurs in normal unanesthetized animals, for the sympathetic which is called into play in preparing the body in emergencies would then act to impede the blood flow through the lungs. Furthermore, in muscular exercise a discharge of impulses over sympathetic paths occurs yet the pulmonary arterial pressure does not rise as it would be expected to do were pulmonary vessels constricted.

systemic blood pressure which occurs in left ventricular failure and in pulmonary embolism.

Inflation and deflation of the lungs within the physiological range causes, respectively, acceleration and slowing of the heart. This respiratory arrhythmia is often very pronounced in young persons (p. 204). The mode of its production has been studied experimentally by a number of investigators. According to Anrep, two mechanisms are concerned, reflex and central. The *reflex* effect is through afferent pulmonary terminals, the *vagus* center and efferent cardiac *vagus* fibers. The impulses set up by inflation cause depression of the tone of the *vagus* center (cardio-inhibitory) with consequent increase in heart rate. The reflex effect is abolished by sectioning either the pulmonary (afferent) or the cardiac (efferent) vagal fibers. The afferent impulses exert no influence upon the cardio-accelerator mechanism, for excision of the stellate and upper thoracic ganglia does not alter the response. The reflex is initiated apparently through the stretch receptors in the visceral pleura or in the layer of lung tissue immediately subadjacent to it. These receptors adapt rapidly and if the inflation is protracted secondary slowing of the heart occurs. Extreme inflation of the lungs causes cardiac slowing rather than acceleration. The slowing of the heart caused by deflation of the lungs is accompanied by depression of auriculo-ventricular conduction; in a heart in which there is already some delay, in conduction over the bundle, deflation may cause complete heart block. The *central* factor in the mechanism leading to cardiac acceleration following inflation is generally believed to be due to the radiation of impulses from the respiratory to the cardio-inhibitory center. It is not abolished by section of the pulmonary fibers of the *vagus* or paralysis of the respiratory movements by means of curare.

THE CIRCULATION THROUGH THE LIVER

The liver receives blood from two sources—from the gastro-intestinal tract, spleen and gall-bladder through the *portal vein*, and from the aorta through the *hepatic artery*.

The portal vein differs from other veins in that it divides into numerous branches which ultimately form a rich capillary network within the liver substance. In this it resembles an artery, but unlike an artery it is interposed between two capillary beds—one, as just mentioned, in the liver, the other in the splanchnic area which it drains. The primary branches of the portal vein upon entering the liver divide into vessels which run between the hepatic lobules (fig. 128). These—the *interlobular veins*—give rise to capillary-like vessels called the *hepatic sinusoids* lying between the liver cords and separated each from a bile capillary by a single layer of hepatic cells. The Kupffer cells (p. 80) are found within the sinusoids, attached by delicate strands to their walls. The sinusoids converge toward

the center of the lobule—like the spokes of a wheel toward its hub—where they empty into a wider channel running perpendicularly to them, and called the *central vein*. The central veins of neighboring lobules join in groups to form *sublobular veins* which unite in turn to form *hepatic veins*. After a series of unions and the formation of larger vessels, the hepatic veins empty into the inferior vena cava.

The hepatic artery is distributed mainly to the fibrous tissue of the capsule and interlobular septa. Its terminal branches join the hepatic sinusoids. The blood conveyed to the liver by the hepatic artery constitutes about 25 per cent of the organ's total blood supply. Upon this fraction, however, the liver depends for its oxygen supply; the oxygen saturation of the portal blood is low and probably gives up little oxygen in its passage through the liver. For this reason necrosis of

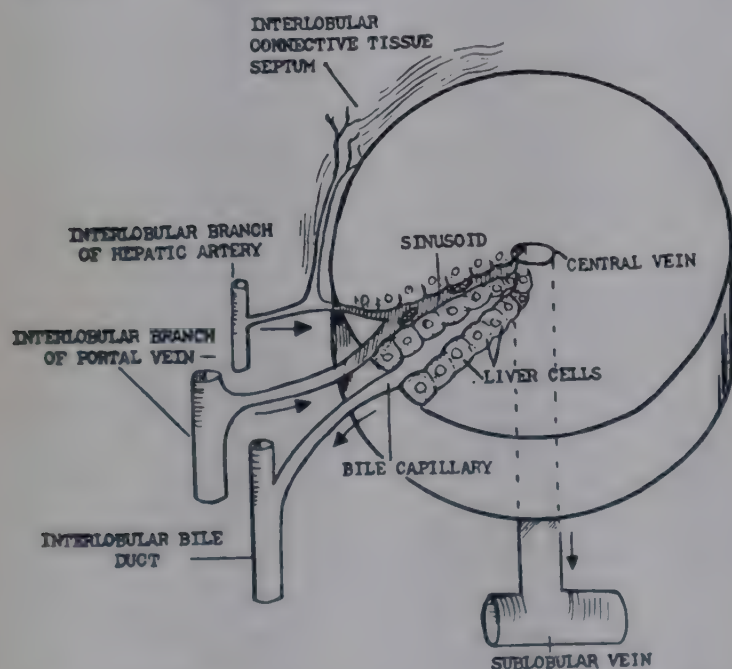


FIG. 128. Diagram of the hepatic circulation. Two Kupffer cells are shown in a sinusoid.

the liver and death follow shortly after ligation of the hepatic artery.

The blood pressure in the portal vein, as measured in experimental animals, is from 8 to 12 mm. Hg. In the dog and probably in man the muscular coat of the hepatic veins near their entrance into the vena cava is highly developed. When contracted the smooth muscle in this situation, which Dale and his associates refer to as the "hepatic sphincter," may cause a marked increase in the resistance to the hepatic blood flow. Through this arrangement the hepatic veins serve the purpose of an adjustable sluice by means of which the quantity of blood in the liver is varied considerably under different conditions. The liver thus functions as a reservoir within which blood at one time may be pooled, or from which at another time an extra quota of blood may be

delivered into the general circulation. Barcroft, Nisimaru and Ray point out, however, that the liver is not a storehouse in the sense that the blood is in a cul de sac and out of circulation, as in the case of the spleen (p. 53). The time taken for a red cell to traverse the hepatic channels (6 to 10 seconds) is only a fraction of the time that it spends in passing through the spleen or even of the skin. It was found, for example, that 30 minutes after an animal had breathed carbon monoxide, samples of blood taken from the femoral artery, portal vein, hepatic veins and from the scratched surface of the liver had all practically the same CO saturation. That is, there had been no greater retention of CO by the hepatic blood, and consequently no significant slowing of the flow through the liver.

The "hepatic sphincter" is constricted by peptone and histamine, and relaxed by adrenaline or sympathetic nerve impulses. The great engorgement of the liver and splanchnic area in dogs following histamine poisoning (histamine shock) is illustrative of the effect of this drug upon the hepatic veins. The splanchnic congestion seen in anaphylactic or peptone shock in this species, is also due, apparently, to constriction of the hepatic veins and the damming back of blood in the portal system. Adrenaline, on the other hand, according to the observations of Rein and his associates, causes the immediate delivery from the liver into the general circulation, of a weight of blood equal to from 26 to 59 per cent of the weight of the liver itself.

The blood flow through the liver is also varied through nervous influences acting upon the intrahepatic vessels and upon the vessels of the splanchnic area. Variations in the caliber of the former will alter the resistance to the flow through the liver. Variations in diameter of the splanchnic vessels, on the other hand, increase or diminish the quantity of blood entering the portal tributaries.

OBSTRUCTION OF THE PORTAL CIRCULATION

In cirrhosis of the liver (portal cirrhosis), the compression of the intrahepatic vessels by fibrous tissue raises the resistance to the flow of blood through the liver. As a result of the rise in pressure in the portal system, the blood is forced into channels, inconspicuous under normal conditions, connecting the portal vein and the systemic veins. The chief among these by-passes for the return of blood from the splanchnic area to the right auricle are provided by anastomoses between

(a) the coronary vein of the stomach and the esophageal veins, (b) the superior hemorrhoidal branches of the inferior mesenteric vein and the middle and inferior branches of the internal iliac (hypogastric) veins, (c) the epigastric veins (superior and inferior) and the portal vein through the para-umbilical vein of Sappey; when these communications are fully established the epigastric veins appear as a group of large tortuous vessels in the abdominal wall in the region of the umbilicus (*caput medusae*); (d) the radicals of the portal vein in the intestines and the inferior vena cava, through the retroperitoneal veins of Retzius.

ECK FISTULA. This is the communication produced for experimental purposes between the portal vein and the inferior vena cava. The two veins are anastomosed side by side and the portal vein then ligated between the anastomosis and the liver; the blood from the portal area is thus turned directly into the vena cava. The hepatic artery is, of course, left intact. This operation has been employed in certain studies where it has been desired to exclude hepatic function. Such an object is not attained, however, for the only satisfactory means of abolishing the function of the liver is to remove it.

EXTIRPATION OF THE LIVER. Ordinarily, death occurs within a very short time after removal of the liver. The rapid death is not due to the loss of the essential hepatic functions, but simply to the fact that since the portal vein must be tied, the return of blood from the splanchnic area to the systemic circulation is blocked. The vessels of the intestines and spleen become intensely engorged, the animal dying as a result of the great reduction in its circulating blood volume, or, as the expression goes, it bleeds into its own splanchnic vessels.

Mann and Magath have devised a three-stage operation which makes it possible to remove the liver completely from dogs and have them survive for periods varying from 20 to 36 hours. The first stage of the operation consists of anastomosing the portal vein and the inferior vena cava and ligating the latter vessel above the anastomosis, but below the entrance of the hepatic veins. All the blood from the lower part of the body is thus directed to the liver. This *reverse Eck fistula*, as it is called, and the consequent great increase in the blood flow to the liver, elevates the portal venous pressure. Anastomotic channels gradually open up between the portal and systemic systems through which a large part of the blood is diverted. After a few weeks when the collateral circulation

has become well established, the portal vein is tied. The final operation, performed after the lapse of another two weeks, consists of tying the hepatic artery and removing the liver, which has now shrunk considerably in size.

Markowitz and Soskin have developed a simplified technique for the removal of the liver which does not involve the anastomosis of the portal vein to the vena cava. They apply ligatures to these vessels which constrict, but do not completely occlude them. The increased resistance thereby induced results in the development of the collateral channels. After these have become established the portal vein and inferior vena cava are completely occluded, and the liver removed in the usual way.

It is also possible to extirpate the liver at one sitting (Markowitz and colleagues) by connecting the infra- and supra-hepatic sections of the vena cava by means of a cannula of pyrex glass (which, as shown by Firor, does not cause blood clotting). The vena cava below the liver is opened. The cannula is inserted into the vein and passed upward through its intra-hepatic portion into the supra-hepatic portion; the vein is then tied around the lower end of the cannula. The portal vein and inferior vena cava are next anastomosed. The vena cava is then tied around the upper end of the cannula. Finally, the portal vein and hepatic artery are ligated and the liver removed, the hepatic tissue being stripped away from the reconstructed vena cava.

THE CEREBRAL CIRCULATION

ANATOMICAL DESCRIPTION

Blood enters the cranium through the *internal carotids* and the *vertebral arteries*. The brain of man receives the greater part of its blood supply through the internal carotids. The two vertebrals unite to form the *basilar artery* which runs forward in the median groove on the under surface of the pons and divides into the two *posterior cerebral arteries*. Each internal carotid divides near the lateral border of the optic chiasma into the *anterior* and *middle cerebral arteries*. Communicating vessels unite the posterior and middle cerebrals on either side and the two anterior cerebrals. Thus a vascular ring—the *circle of Willis*—is formed at the base of the brain around the optic chiasma, the tuber cinereum, infundibulum and corpora mammillaria. Through the circle of Willis very free communication between the internal carotids and the vertebrals is established. Owing to the presence of these anastomotic channels both carotids can be tied in the monkey without serious interference with the blood supply to the brain. Ligation of both carotids and one vertebral in this animal results in stupor and death. The dog survives after both internal carotids and the two vertebrals near their origins have been ligated. Blood then reaches

the circle of Willis through anastomoses between the spinal branches of the vertebrals and the deep cervical artery; and also, as shown by Bouckaert and Heymans, through an ophthalmic branch of the internal maxillary artery (branch of external carotid) which communicates with the internal carotid within the skull. This latter communication is capable of maintaining the viability of the brain, though all other channels through which blood could enter the cranial cavity have been tied. The extent to which the main arteries to the human brain can be occluded is not definitely known. In most instances, ligation of one common carotid in man causes no ill effects owing to the rich anastomoses between the two external carotid and between the external carotid with the internal carotid of the opposite side. Syncope, convulsions, etc. reported as resulting from compression of one common carotid were in all probability due to a sinus reflex (p. 241) rather than to mechanical interference with the cerebral blood supply. Compression of both common carotid arteries in man is followed within a few seconds by unconsciousness.

The anterior and middle cerebral arteries, branches of the internal carotid, and the posterior cerebral branches of the basilar, after giving off branches which supply chiefly the basal ganglia and hypothalamus, pass to the surface of the cerebrum. Here they ramify in the pia mater and send twigs into the underlying substance of the hemispheres. The anterior cerebral courses forward from its origin to the commencement of the longitudinal fissure and then arches backward over the corpus callosum. It is distributed over the medial surface of the frontal and parietal lobes; an adjacent band of cortex on the lateral aspect of the hemisphere; and the cortex of the cingulate gyrus. The middle cerebral artery reaches the surface of the hemisphere through the Sylvian fissure. Among its basal branches are twigs—*lenticulo-striate*—to the lentiform nucleus and internal capsule. One of these, larger than its fellows, not infrequently ruptures and on this account is referred to as the "artery of cerebral hemorrhage." The cortical distribution of the middle cerebral includes the anterior pole of the temporal lobe; the lateral part of the orbital surface of the frontal lobe, the insula; and the large area of the lateral surface of the hemisphere not supplied by the anterior or posterior cerebrals, that is, the greater part of the middle and inferior frontal gyri; the lower two-thirds of the pre- and post-central gyri; the supramarginal and angular gyri; and the superior and middle temporal gyri. The posterior cerebral artery curves backwards between the cerebral peduncle and the uncus. It supplies the uncus and hippocampal gyrus on the medial aspect of the hemisphere, the fusiform and inferior temporal gyri, and the cortex on the medial, inferior and lateral surfaces on the occipital lobe.

The vertebral artery on each side gives off a little below the pons a *posterior inferior cerebellar* branch which supplies the medulla. It sends twigs to the glossopharyngeal, vagus and accessory nuclei; to the

spino-thalamic, spino-cerebellar and rubro-spinal tracts; and, probably, to the spinal root of the trigeminal nerve. The basilar artery, formed by the union of the two vertebrals gives off on each side an *anterior inferior cerebellar* branch which ramifies over the under surface the cerebellar hemisphere, and a *superior cerebellar* branch which is distributed to the superior surfaces of the vermis and cerebellar hemisphere.

The blood is returned from the brain through the *cerebral veins* which course over the surface of the hemispheres, and receive as tributaries the small veins which drain the capillary bed in the brain substance. The cerebral veins drain into the large *dural sinuses*—*superior and inferior sagittal, cavernous, straight*, etc.—which lie enclosed between the outer and inner layers of the dura mater. The sinuses possess no valves. Their triangular cross-section and the support afforded by their dural envelopes render them relatively resistant to compression. The venous blood ultimately finds its way into the two *transverse sinuses*. The transverse sinus on either side becomes continuous at the jugular foramen with the internal *jugular vein*.

The network of veins which begins with the dural sinuses in the posterior cranial fossa forms a longitudinal plexus which extends throughout the entire length of the spinal column and communicates at each intervertebral space with veins within the thorax and abdomen. This plexus constitutes a route through which the blood can be returned from the cranial cavity to the superior and inferior venae cavae. That this alternative channel is of great functional importance in man is shown by the fact that both internal jugulars can be ligated simultaneously without serious consequences. Even complete occlusion of the superior vena cava by a thrombus may occur with relatively little ill-effect. Other less important channels through which blood may be returned from the cranium are, the emissary veins of the skull which connect the dural sinus with the veins of the scalp, and communications between the veins of the orbit and the pterygoid plexus of veins.

The gray matter is much more vascular than the white matter. In the human cerebral cortex the total capillary length is about 1 meter per cu. mm. of tissue, and only around 200 mm. per cu. mm. in the underlying white substance. The cerebral vessels are not "end arteries" but form a continuous, freely communicating network through which a corpuscle might travel from the frontal to the occipital lobe.

FACTORS REGULATING THE CEREBRAL BLOOD FLOW

The adult cranial cavity and vertebral canal form a space which is almost completely enclosed by rigid walls and filled by brain substance, cerebro-spinal fluid and blood. The total volume of the cranial contents, which are incompressible, can therefore alter relatively little and to an extent which is determined simply by the degree of

bulging of the membranes at the occipito-atlantoid joint and between the vertebrae.⁷ Nevertheless, under certain circumstances considerable reciprocal volume changes between the brain substance, cerebro-spinal fluid and blood may occur. The intravenous injection of hypertonic (30 per cent) saline, for example, causes, through the changes in osmotic relationships, a shrinkage of the brain, a fall in cerebro-spinal fluid pressure from around 10 mm. Hg to a negative value (-10 mm. Hg), but a very moderate fall in the pressure of blood in the superior sagittal sinus. As a consequence, reversal of the normal relationship between cerebro-spinal fluid and venous cerebral pressures results, the former being reduced considerably below the latter. The creation in this way of a negative cerebro-spinal fluid pressure is strong evidence that the cranial contents are contained within a "closed box." Hypotonic solutions cause an increase in brain volume and a rise in cerebro-spinal fluid pressure and of the pressure in the superior sagittal sinus; the normal relationship between cerebro-spinal fluid and cerebral venous pressures is therefore maintained.

The vessels of organs such as the kidney, liver or muscles, etc., can dilate widely and the whole organ expand (see fig. 114, p. 252). Consequently a greater mass of blood can be held by these structures at one time than at another, and it is possible for a greater volume of blood to flow through them without the velocity of flow through the individual vessels being increased. Since the mass of intracranial blood cannot be much greater at one moment than another, a greater oxygen supply to the brain is assured largely by an increase in the speed of the blood through the individual vessels rather than by an enlargement in the total capacity of its vascular bed. The cerebral circulation time (carotid to jugular by the radium emanation method) is around 3 seconds.

The velocity of the blood through the intracranial vessels is determined by the pressure difference (pressure gradient) between the cerebral arteries and the cerebral veins. The pressure in the former vessels is ordinarily proportional to the systemic arterial pressure. The pressure in the larger cerebral arteries is about 65 mm. Hg

diastolic, and 100 mm. Hg systolic. The pressure in the capillaries is about 13 mm. Hg. The pressure in the intracranial veins though lower than, varies with, the cerebro-spinal fluid pressure. The venous pressure in the recumbent position is from 6 to 8 mm. Hg, i.e., approximately the same as the pressure in the median basilic vein, but becomes reduced nearly to zero in the erect position. Changes in venous pressure at the right auricle are transmitted to the jugular vein and so to the intracranial veins. In consequence, the pressure in the venous sinuses varies as a result of the changes in intrathoracic pressure occurring during the respiratory cycle—increasing during expiration and decreasing during inspiration. Failure of the right ventricle, thrombosis of the transverse sinus or obstruction of the jugular vein, or of the superior vena cava, are among some of the pathological conditions which result in an increase in the cerebral venous pressure. A fall in arterial pressure or a rise in cerebral venous pressure will tend to slow the blood flow through the brain; reverse changes will tend to increase the cerebral blood flow. However, apart from the postural and respiratory variations just mentioned the cerebral venous pressure remains fairly constant under ordinary conditions. The intracranial blood flow is, therefore, determined largely by the height of the general arterial blood pressure. Until recently this was considered to be the sole factor regulating the flow through the brain; the cerebral vessels themselves were thought to play a purely passive rôle.

Next to the systemic blood pressure, the gas tensions of the blood constitute the most important factors in the control of the cerebral circulation. Carbon dioxide has a profound dilator effect upon the pial vessels; it is capable of causing changes in vascular calibers independently of alterations in the general blood pressure, and by dilating the vessels may increase the cerebral blood flow by 40 per cent. Anoxemia has been found by most investigators to exert a much less potent vasodilator effect; an increase in oxygen tension causes a slight decrease in blood flow through the brain.

The results of Schmidt's investigations have thrown doubt upon the generally held view that carbon dioxide is a powerful dilator of the cerebral vessels. The experiments upon which this belief is based were mostly upon cats and total cerebral blood flow was not determined. Dumke and Schmidt measured the total blood flow in the monkey and found that raising the CO_2 content

⁷The conception of the invariability of the volume of the intracranial contents as a result of the rigidity of the cranial boundaries, originated with Alexander Monro of Edinburgh (1783), and was elaborated by Kellie (1824); it is therefore commonly known as the Monro-Kellie doctrine.

of the inspired air only slightly increased the cerebral blood flow, and that changes in the oxygen content caused more consistent and more pronounced effects. These results have been confirmed, and mean either that previous determinations of changes in blood flow in the cat were not representative of what occurs in the vessels of the brain as a whole, or that species difference exists. If the latter alternative is the correct one, since man is closer philogenetically to the monkey than to the cat, the experimental results of these authors are of greater importance.

THE NERVOUS CONTROL OF THE CEREBRAL VESSELS. Gulland nearly forty years ago (1898) reported having discovered nerve filaments upon the blood vessels of the pia mater; Huber a year later described medullated and non-medullated nerves ending on these vessels. He considered the medullated filaments to be sensory, the non-medullated, vasomotor in function. Nerve fibers going to the blood vessels within the brain substance have also been described by others (Kolliker, Clarke) and more recently by Penfield.

Though Wiggers had demonstrated that the pial vessels reacted to adrenaline by constriction, it is only within the last few years that definite evidence of the nervous control of the intracranial vessels has been secured; it is now definitely established that vasoconstrictor impulses are conveyed by the sympathetic; vasodilatation follows stimulation of the central end of the vagus (see below).

The pial vessels have been observed by Forbes and Wolff through a glass window screwed into a trephine hole in the skull, the space between the glass and the brain surface being filled with Ringer's solution. Upon stimulation of the sympathetic, constriction of pial and dural vessels was observed accompanied by a rise in systemic arterial pressure; section of the sympathetic was followed by dilatation of the exposed vessels. Stimulation of the central end of the cut vagus, aortic or sinus nerves or of the facial nerve at the geniculate ganglion, resulted in dilatation of the pial vessels and a fall in systemic pressure. The vessels of the pia mater were not altered in caliber by a rise in the systemic arterial blood pressure unless this exceeded 60 mm. Hg; dilatation of the vessels apparently passive in nature was then observed. These experiments show that the superficial cerebral vessels can constrict or dilate quite independently of, or indeed in spite of, a rise or a fall in systemic pressure, and prove conclusively the existence of a nervous mechanism

in the control of the intracranial circulation. This control is not essentially different from that governing the caliber of the systemic vessels except that the cerebral vessels, according to Schmidt, are held in a state of tonic dilatation rather than in one of tonic constriction as prevails in the vascular system of the rest of the body. Reduction of vasodilator tone is probably of greater importance than sympathetic impulses in bringing about constriction of the cerebral vessels.

A fall in systemic blood pressure below a certain critical level (about 60 mm. Hg) causes dilatation of the cerebral vessels. This reaction apparently constitutes a safety device to maintain an adequate blood supply to the brain. The associated fall in blood pressure has been shown to be the factor responsible for the vasodilatation caused by stimulation of the vagus, aortic or sinus nerves (Forbes and associates), for vasodilatation fails to take place if the blood pressure is prevented from falling while the nerve is stimulated. On the other hand, the vasodilator response is not altered by the application of cocaine to the pial vessels, which indicates that it is not a true reflex but a reaction of the vascular walls themselves to the low intravascular pressure. Since vasodilatation following vagal excitation is simply a compensatory response to the fall in blood pressure it rarely causes any increase in cerebral blood flow. The cerebral vasodilatation caused by stimulation of the facial nerve occurs with a normal blood pressure and is abolished by cocainization of the pial vessels. It therefore appears to be a direct reflex response of the vessels to nerve stimulation. The vasodilator fibers of the facial pass to the vessels via the geniculate ganglion, the great superficial petrosal and the internal carotid nerves. *The facial is apparently the only nerve carrying dilator fibers to the cerebral vessels.*

The observations just described are not incompatible with the conception that the quantity of blood within the cranial cavity remains *approximately* constant. For, changes in the calibers of the vessels in one area of the brain may coincide with changes of an opposite character in another,*

* A number of observations support the idea of regional variations in cerebral blood flow in accordance with functional demands. For example, Fulton observed in a patient that the blood flow of a vascular tumor (hemangioma) of the occipital lobe increased (as indicated by an accentuation of the bruit heard over the occipital bone) when the subject read fine print. Also, in animals a thermocouple in the optic pathway records a rise in temperature when the eyes are illuminated; on the other hand, when the skin of

and, since the spinal column does not constitute a completely rigid encasement but contains distensible structures, small reciprocal changes in cerebro-spinal fluid may allow corresponding variations in vascular diameters. During sympathetic stimulation an average reduction in diameter of 8.5 per cent occurs and during vagal stimulation an average increase in diameter of 22 per cent. The dilatation of even a relatively large number of arterioles to this extent might cause little increase in the total quantity of blood contained at any instant within the cranium. Nevertheless, a very considerable increase in blood flow might result, for, according to Poiseuille's law (p. 114) the flow of liquid through a capillary tube (other factors remaining constant) is directly proportional to the fourth power of the diameter of the tube. Thus an increase of 22 per cent in vascular diameters would increase the blood flow 150 per cent (Cobb).

These facts throw a new light upon the physiology of the cerebral circulation. They indicate that with a constant systemic arterial blood pressure, changes in blood flow not only through one part of the brain in relation to another part, but through the brain as a whole may be brought about. Finesinger and Putnam, for example, perfused the brains of monkeys through the internal carotid with heparinized blood after tying the vertebrals and the opposite carotid. The minute volume of the inflow was measured while the sympathetic or vagus was stimulated, the perfusion pressure being maintained constant. Sympathetic stimulation reduced and vagal stimulation increased the inflow. It was found, however, that variations in the perfusion (carotid) pressure were more effective in varying the blood flow than was nerve stimulation with a constant pressure head. The maximum blood flow through the brain would of course result from a rise in systemic pressure accompanied by dilatation of the cerebral vessels. In this connection may be cited the observations of Heymans and Bouckaert. These observers found that a pressor reflex elicited from the carotid sinus did not involve the cerebral vessels. In this reflex the rise in blood pressure, due to vasoconstriction of the

the feet was stimulated, though there was no indication of increased flow in the optic pathways, a definite temperature rise was recorded from nervous tracts subserving cutaneous sensations (Gerard and Serota) and, during muscular movements, from the motor cortex. Increased vascularity, as demonstrated by intravital injections of dye, is found in the olfactory lobes of the cat after the inhalation of a strong-smelling gas.

systemic arterioles, must obviously result in a greater flow through the cerebral vessels than would occur if these shared in the vasomotor response.

Alterations in the blood flow through the human brain can be determined from comparisons of the oxygen (or carbon dioxide) contents of the blood entering and leaving the cranial cavity. Blood samples are taken from an artery and the jugular vein. An increase in the arterio-venous oxygen (or carbon dioxide) difference⁹ indicates a reduced blood flow; a lowered arterio-venous oxygen (or carbon dioxide) difference (i.e., jugular blood more arterial in character) indicates an increased flow. Variations in the intracranial blood flow of the human subject can also be demonstrated by inserting an electrically heated needle into the jugular vein, and measuring fluctuations in its temperature by means of thermocouples connected in series with a galvanometer. The heated element is cooled by the blood flowing around it, a rise or fall in its temperature, therefore, indicates a reduced or an increased blood flow respectively.

Ferris has attempted to measure the total blood flow through the human brain by an ingenious plethysmographic method (see p. 149). A wide-bore needle is introduced into the lumbar subarachnoid space, the cerebral blood flow is estimated from the displacement of cerebrospinal fluid while the jugular veins are occluded for a brief period by means of a pressure cuff encircling the neck. The total cerebral blood flow in man, as measured by this method, is 250 cc. per minute during rest and 400 cc. maximum, or 16 cc. and 26 cc. per 100 grams of brain substance per minute. Owing to certain sources of error in this method (e.g., the escape of blood from the craniovertebral cavity through unoccluded veins) this estimate is probably much too low. Dumke and Schmidt obtained a higher figure for the monkey, namely, 60 and 110 cc. per 100 grams of brain per minute.

The demonstration that the cerebral vessels can vary their calibers independently of changes in systemic blood pressure also provides a physiological basis upon which temporary disturbances in cortical function may possibly be explained. It has long been suspected, for example, that transient hemiplegia, amblyopia, and possibly migraine or convulsive seizures, may be due to

⁹ Under ordinary circumstances this is high, namely, about 8 volumes per cent (coefficient of oxygen utilization around 0.4).

spasm of pial vessels and a consequent anemia of the cerebral centers. Attempts to gain information upon this question have been made by studying the effects of convulsant poisons in animals. Finesinger and Cobb observed acute constriction of the pial vessels preceding the convulsions induced by the intravenous injection of caffeine; but only vasoconstriction preceded the convulsions caused by the administration of picrotoxin or small doses of absinthe and vasodilatation resulted from the administration of a convulsive dose of camphor or of a large dose of absinthe. Nor does it appear that the convulsive action even of those drugs which cause pial vasoconstriction is directly due to reduced cerebral blood flow. Gibbs, for example, found that convulsions followed the administration of caffeine though the blood flow was increased by injecting adrenaline (see below). The general belief that cerebral anoxia causes an initial stimulation of nervous tissue with the production of convulsions, has been disputed by Schmidt who maintains that oxygen lack always depresses cerebral functions.

THE ACTIONS OF CERTAIN CHEMICALS AND DRUGS UPON THE CEREBRAL VESSELS

Histamine dilates the pial vessels and raises the cerebro-spinal fluid pressure. Flushing of the cortex has been observed in man following its administration; this is probably the cause of the intense but transient headache which sometimes follows an injection of histamine. Weiss and Lennox showed also that the arterio-venous oxygen difference was reduced, i.e., the intracranial blood flow was increased, by histamine. Since the systemic blood pressure remained practically unaltered, dilatation of the cerebral vessels must have occurred. *Metrazol*, *ether*, *alcohol* and *carbon monoxide* are also dilators of the pial vessels. *Adrenaline* applied locally to the surface of the brain causes vasoconstriction. Its injection into the general circulation, however, is followed by vasodilatation. This is a passive effect due to the rise in blood pressure, that is, the latter overcomes the local effect of the hormone upon the pial vessels. The net result of adrenaline liberation under physiological conditions is therefore an increase in cerebral blood flow. *Benzedrine* given by intracarotid injection reduces the blood flow to the brain. *Pitressin* has an inconstant effect but in most instances causes cerebral vasoconstriction. *Acetylcholine* is vasodilator but, owing to its causing a coincident fall in blood pressure, little or no increase in blood flow results; it may even cause a reduction. Most *anesthetics*, especially *ether*, cause vasodilatation. *Hypertonic solutions* administered intravenously cause a brief period of vasoconstriction followed by an increased blood flow. This is apparently due to the well-known action of such solutions in reducing the intracranial pressure and in causing a rise in systemic arterial pressure. *Caffeine* in large doses decreases the cerebral blood flow. *Amyl*

nitrite dilates the cerebral arterioles as it does those of the rest of the body. There are very few agents known which constrict the cerebral vessels. Among them are *barium chloride* and, as already mentioned, a high tension of oxygen. A low CO_2 tension, of course, results in vasoconstriction.

THE EFFECT OF INCREASED INTRACRANIAL PRESSURE UPON THE CEREBRAL CIRCULATION

Forbes and Wolff studied in cats the effects upon the cerebral circulation of raising the intracranial pressure. They introduced Ringer's solution under pressure into the cisterna magna and observed the superficial vessels through a glass window fixed into the cranial wall. It might be thought that any considerable rise in intracranial pressure would compress the cerebral veins and arrest the circulation. No change in the vessels of the pia mater could be detected, however, until the cerebro-spinal fluid pressure had been increased to a value four or five times that of the normal. With gradual elevation of the pressure the sequence of vascular events was;—slowing of the blood flow in the veins, then dilatation of their lumina; dilatation of the arteries, slowing of the arterial blood flow, narrowing of the arteries; and finally, complete obliteration of the vessels with consequent blanching of the cortex. It appears that as the cerebro-spinal fluid pressure rises, the pressure is transmitted to the blood in the veins and through these vessels to the capillaries and arteries. Thus, though at first no change in systemic arterial pressure occurs, a higher arterial pressure is established within the cranium and the difference between arterial and venous cerebral pressures is maintained. The cerebral circulation, though slowed, is able to continue despite a high cerebro-spinal fluid pressure. When the cerebro-spinal fluid pressure equals the systemic arterial pressure the circulation through the cerebral vessels, of course, becomes impossible.

The "local" rise in arterial pressure accounts for the fact that in clinical cases in which, though the intracranial pressure is considerably elevated and the systemic arterial pressure unaltered, the circulation through the brain is not cut off. It has been shown by Berens and his associates that in subjects of brain tumor a rise in the pressure in the retinal arteries may occur unaccompanied by any elevation of the systemic pressure. When the cerebro-spinal pressure continues to rise and the pressure in the cerebral arteries approaches that in the systemic vessels, the intracranial blood flow must be seriously curtailed and finally arrested unless further adjustments occur. These are brought about through the vasomotor center; the slowing of the flow through the medulla stimulates the center; a rise in systemic blood pressure results to force blood through the cerebral vessels threatened with obliteration.

SECTION III. RESPIRATION

CHAPTER XXIX

INTRODUCTION

THE MECHANICS OF RESPIRATION

The term "respiration" refers to the gaseous interchange between an organism and its environment. The more obvious chemical features of this process are the absorption of oxygen and the elimination of carbon dioxide. All living things, excluding certain microorganisms which secure energy from dehydrogenase or similar systems, must be supplied with oxygen. The oxygen is absorbed by the blood in the lungs for delivery to the tissue cells wherein carbon is oxidized to carbon dioxide and hydrogen to water. The CO_2 is transported by the blood to the lungs and eliminated in the expired air. The exchange of the respiratory gases between the tissue cells and the internal environment, which is constituted by the fluids bathing the cells, is called *internal respiration*. This process is essentially the same as that taking place between unicellular organisms (e.g., the amoeba) or primitive multicellular forms and the aqueous environment in which they live. The exchange of oxygen and carbon dioxide between the blood in the pulmonary capillaries and the air in the lungs is termed *external respiration*. The study of respiration therefore involves, principally, (1) the physiological mechanisms responsible for the body obtaining an adequate supply of oxygen from the external environment, (2) the transport of oxygen from the lungs to the tissues and of carbon dioxide to the lungs, (3) the exchange of the respiratory gases between the cells and the internal environment, (4) the oxidative and other respiratory processes within the tissue cells whereby energy is liberated, and (5) the control of these mechanisms and their correlation with one another and with other bodily processes.

Physiological anatomy

Air entering through the nasal openings is warmed and some of the grosser impurities are retained by the fine hairs around the nostrils and by the mucous secretion. The nasal cavity just within the external nares (vestibule) is lined with skin. The remaining parts of the nasal cavities are lined with mucous membrane which is covered by a layer of ciliated columnar epithelial cells and scattered "goblet" cells; it is continuous

with the membrane lining the accessory nasal sinuses. (The nasal lining is very vascular; it contains a venous plexus whose channels anastomose freely and give the mucosa an appearance suggestive of erectile tissue. The vascular channels are dilated by several conditions, e.g., infections, local irritants, certain anaphylactoid states and a rise in temperature of the inspired air; the mucosa swells and the airway is narrowed in consequence. Cooling the inspired air causes their constriction, as will also the application of adrenaline or ephedrine to the mucosa. The vascularity of the mucosa is also influenced reflexly by the application of heat or cold to the skin of remote regions of the body.) Leonard Hill has postulated a remarkable effect of infra-red rays applied to the skin in altering the diameter of the nasal airway. The effective or "nose closing" rays are said to be those given out by a dull red or dark source of heat (waves over 30,000 Ångström units in length). The interpretation of these results and others more recently reported by Hill on "nose opening" rays has been seriously challenged by other workers in this field. The present position is that the problem awaits thorough investigation. [The pharynx is, of course, a common pathway for food and air. As the food passes the laryngeal opening this is closed by reflex action and respiration is inhibited. The surface epithelium of the nasal part of the pharynx is provided with cilia and goblet cells. In the oral part of the pharynx the epithelium is of the stratified squamous type. The epithelium of the bronchial tree presents very definite changes as one proceeds from the larynx to the terminal bronchioles. The stratified squamous covering of the upper part of the larynx changes to ciliated in the lower part of the vestibule of this organ. The vocal cords are covered with squamous epithelium, but ciliated cells again line the trachea. The epithelium of the trachea contains also goblet cells and mucous and serous glands. The large bronchioles are similar to the trachea in this respect, but in the bronchioles the goblet cells and deep glands are lost.]

CILIA. The nasal secretions are moved toward the nostrils mainly by the action of cilia. It is perhaps not generally appreciated that the sinuses are kept clear, under normal conditions, by the beating action of the cilia with which the epithelium is very plentifully supplied. As stated above, ciliated cells are found in the nasal part of the pharynx, in the lower part of the vestibule of the larynx and in the trachea.

The cilia beat with a motion which propels material toward the mouth. They become even more abundant when the large bronchioles are reached, but are largely replaced by cuboidal or flattened cells in the respiratory bronchioles.

The efficiency of the ciliated cells of the trachea and large bronchioles in propelling mucus and waste material orally is, under normal conditions, of a high order. The cilia are not influenced by nerve impulses, but are very susceptible to chemical changes in the blood and to substances applied locally. Certain general anesthetics depress their activity and many sedatives exert the same effect. Ciliary action is depressed by cold and increased when the temperature of the cells is

probably in large part for the recoil mechanism of the whole lung. The importance of this elastic recoil will be stressed again later. In the larynx, cartilage supports the special structures necessary for the attachment of the vocal cords and the functioning of the glottis. The cartilaginous rings in the trachea are incomplete on the posterior aspect. This arrangement provides for some contraction of the trachea, but the lumen cannot be obliterated as is the case with the small bronchioles.

MUSCLE. The ends of the cartilaginous rings of the trachea may be approximated by the action of the transverse smooth muscle fibers. In the bronchi the bands of fibers tend to become circular and this is seen

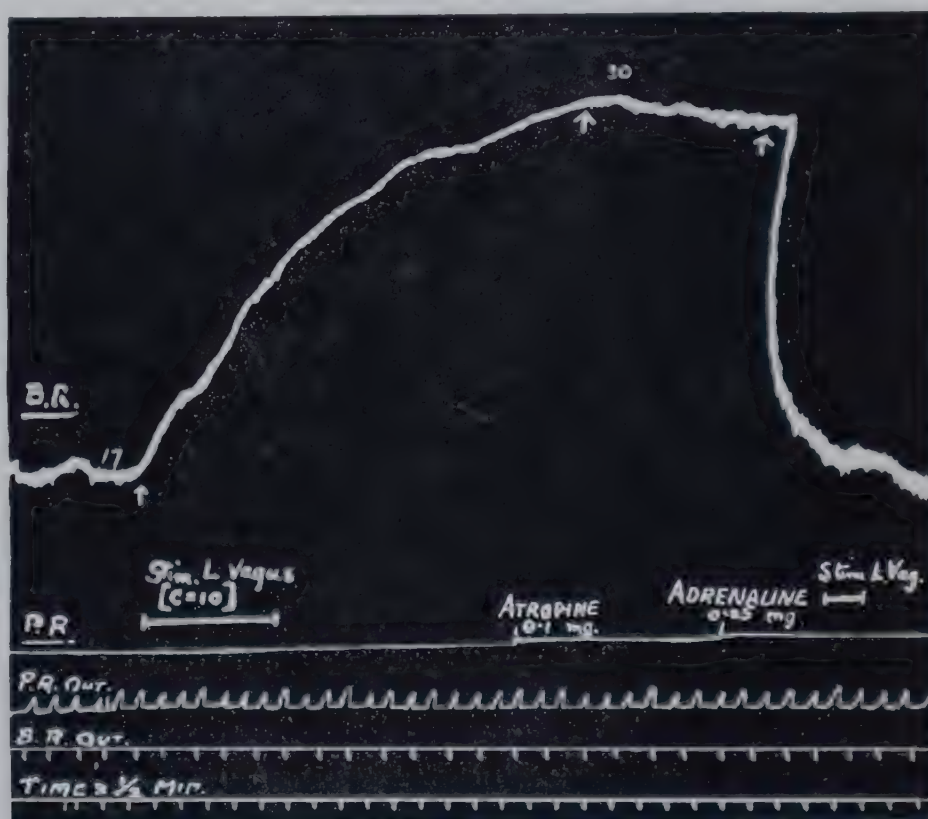


FIG. 129. Guinea-pig. Showing the broncho-constrictor effect of stimulating the vagus of the same side. The effect lasts after stimulation has ceased. Atropine in moderate dose had a very slight dilator action; adrenaline in small quantity caused marked bronchodilatation. During this action further stimulation of the vagus had an almost negligible effect. (After Thornton.)

raised slightly above normal. The efficiency of the cilia depends in part on the viscosity and stickiness of the material which is in contact with them. Their effectiveness may be varied by changing the properties of this material as well as by increase or decrease in the rate or force of beating. The motion of the cilia is wave-like and has been well compared to the undulation of a field of wind-swept grain. The individual cilium moves, in the direction in which its force is exerted, with a whip-like motion and then relatively slowly returns to its former position.

ELASTIC TISSUE. The bronchial tree is rich in elastic tissue, most of the fibers being disposed longitudinally in the tunica propria. This elastic membrane, which extends throughout the trachea, bronchi and bronchioles right to the alveoli, is responsible for the recoil of the bronchial tree during expiration and

even more definitely in the bronchioles. The amount of muscle is reduced in the respiratory bronchiole and does not extend beyond this subdivision of the bronchial tree.

BLOOD SUPPLY. The bronchial tree, as far as and including the respiratory bronchioles, is supplied by a rich plexus of vessels derived from bronchial arteries—branches of the thoracic aorta. The blood is collected by the bronchial veins which in the case of the right lung empty into the azygos vein. Those from the left lung are tributary to the left superior intercostal vein (or sometimes to the accessory hemiazygos vein). The respiratory part of the lung receives its blood from the pulmonary artery, the blood being returned via the pulmonary veins to the left side of the heart. Anastomoses between the pulmonary and systemic systems of vessels occurs, however, in the walls of the

respiratory bronchioles, so that the blood from this region of the bronchial tree is returned in part to the right side of the heart and in part to the left.

NERVE SUPPLY OF THE BRONCHIOLES. Excitor (broncho-constrictor) fibers to the bronchiolar muscle are derived from the vagus, and inhibitor (broncho-dilator) fibers from the sympathetic. Afferent fibers from the lungs run in the vagus. The nerve supply to the pulmonary vessels is considered on page 284. The bronchioles are constricted by pilocarpine, histamine and by certain foreign proteins (anaphylactic reactions). They are dilated by adrenaline, ephedrine and atropine (figs. 129 and 166, p. 368).

THE BRONCHIOLES AND AIR SACS. Macklin divides the bronchial tree into two parts. The first part which extends from the trachea to the *terminal bronchiole* inclusive, serves simply as an air-conduit and, like the branches and twigs of a tree, possesses no respiratory function. The terminal bronchiole is simply the last of a series of subdivisions of these non-respiratory bronchioles. The muscle in its wall is more highly developed than in any other part of the bronchial tree and when fully contracted exerts a sphincter-like action which can completely shut off the air supply to the air chambers beyond.

The structures lying distal to the terminal bronchiole are the "leaves" of the bronchial tree. They are respiratory in function, i.e., an interchange of gases between lung air and blood occurs across their walls. This part consists of (a) the *respiratory bronchioles*, (b) *alveolar ducts*, (c) *alveolar sacs*, and (d) *pulmonary alveoli*. The cluster formed of these structures together constitutes a *lung-unit* or *primary lobule* (i.e., the group of structures which like the nephron or renal unit carries out the specific function of the organ). It is the distensible or bellows part of the lung.

The *respiratory bronchiole* has the same diameter as the terminal bronchiole, of which it appears as a branch or a continuation. The *alveolar ducts*, five or six in number, arise from each respiratory bronchiole (fig. 130). Each alveolar duct after a variable number of rebranchings gives rise to from 3 to 6 dilatations, the *alveolar sacs*. The bays in the walls of the latter constitute the *pulmonary alveoli* which are lined by a single layer of flattened epithelial cells cemented together. The alveolar walls contain elastic fibers and a rich network of capillaries. Frequently a single capillary channel alone intervenes between the walls of adjacent alveoli. The blood in the capillaries is therefore separated from the air in the alveoli by two membranes of the utmost delicacy—the alveolar and capillary walls—so the greatest freedom is afforded for the diffusion of gases from the blood to the alveolar air and from the alveolar air to the blood (Willson; Macklin).¹

¹ The results of Josselyn's recent studies on the anatomy of the alveoli strongly suggest that the alveolar lining may be a discontinuous membrane and that the capillaries are uncovered. In certain areas,

The bronchioles, as they are traced toward the periphery of the lung, branch and rebranch repeatedly, diminishing in length with each subdivision. The first branchings are about 1.5 mm. in length and from 0.3 to 0.4 mm. in diameter. The terminal and respiratory bronchioles are from 0.2 to 0.5 mm. in length, but of about the same diameter as the earlier subdivisions. That is, the bronchioles, though becoming shorter, show practically no decrease in diameter as they pass toward the periphery. The alveolar sac, however, is considerably wider than the respiratory bronchiole or than the alveolar duct from which it arises. The diameter of each pulmonary alveolus which has a semi-globular form is from 0.075 to 0.125 mm. and the total number in the lungs has been estimated by Zuntz at

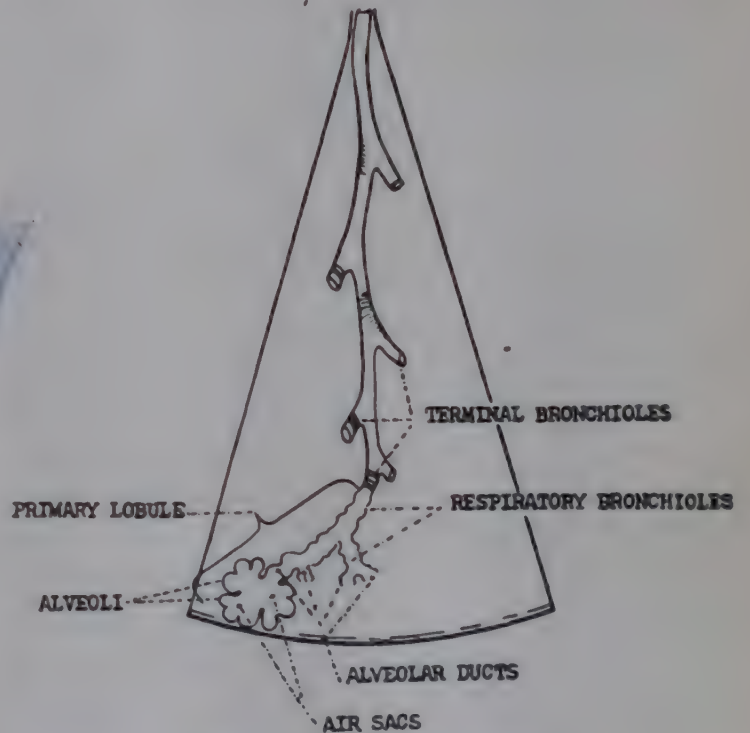


FIG. 130. Description in text.

750 millions. Willson estimates the total epithelial surface of the lungs at 70 square meters. Of this, probably 55 square meters is respiratory; this is over 25 times the surface area of the skin (p. 534).

THE EXPANSION OF THE LUNGS AT BIRTH

Before birth the alveoli contain a small quantity of fluid; the thorax is unexpanded and completely filled by the quite airless lungs. At this time only a small part of the blood of the right heart passes through the lungs. The remainder passes by the ductus arteriosus into the aorta and via the foramen ovale in the interauricular septum to the left heart. Respiratory movements are made by the fetus *in utero*, a fact clearly demonstrated by the work of Barcroft and of Snyder and Rosenfeld. India ink injected into the amniotic sacs of

therefore, the air in the alveoli would be separated from the blood only by the capillary endothelium and a small amount of fluid.

rabbits was found in the alveoli. A movement of amniotic fluid into and out of the fetal lungs appears to be a normal event and probably plays an important rôle in the dilatation of the future air passages. Movements at a rate of about 60 per minute have been observed in the human fetus which are evidently of the same character as those demonstrated in animals. The movements are readily inhibited, especially by anoxemia and narcotics. They are depressed by CO_2 deficit. At the moment of birth the respiratory movements become more forceful, the diaphragm descends and the external intercostal muscles contract with the result that the diameters of the thoracic cavity are very considerably increased (p. 505). A large proportion of the venous blood is now conveyed through the lungs. (The general enlargement of the capacity of the thorax—a closed cavity—tends to reduce the pressure on the outer (pleural) surfaces of the lungs. The greater the degree of enlargement of the chest, the greater will be the reduction in the pressure upon the outer pleural surfaces of the lungs.) The interior of the lungs, however, is in direct communication, through the air passages, with the atmosphere. The visceral and parietal pleurae being inseparable the lungs follow the thoracic wall as it enlarges, and therefore must expand. The rarefaction of the pulmonary air as a result of the expansion results in a flow of atmospheric air into the lungs. Full expansion of the lung is not attained until some few days after birth. The lung throughout the individual's life remains in the expanded position—pressed as it were against the thoracic framework as a result of the greater pressure exerted upon the alveolar than upon the pleural aspects of the pulmonary tissue (p. 298).

Rhythmically alternating increases and reductions of the expanded state of the lungs initiated at birth continue throughout life and constitute respectively the *inspiratory* and *expiratory* phases of respiration. The alternate inflations and partial deflations of the lung are the direct result of corresponding changes in the capacity of the thoracic cavity occasioned by the movements of the diaphragm and other respiratory muscles. Changes in pressure within the lung—the *intrapulmonary pressure*—and upon its pleural surfaces—the *intrapleural pressure*—occur coincidentally with the alterations in lung volume.)

INTRAPULMONARY PRESSURE. In the resting position of the chest the intrapulmonary pressure is atmospheric, but it varies rhythmically with the phases

of respiration, rising above atmospheric pressure during expiration and becoming subatmospheric during inspiration. These variations may be demonstrated by connecting one nostril with a manometer and breathing with the mouth closed. The pressure will be found to be about -2 mm. Hg during the inspiratory phase and to rise to $+3$ or $+4$ mm. Hg during the expiratory phase of ordinary quiet respiration.² The variations are accentuated considerably during forced respiration. The maximal negative pressure capable of being developed within the lungs by a forced inspiration, as when a strong sucking effort is made, is from -40 to -50 mm. Hg. When expiratory efforts are made against a closed glottis, as in coughing, during muscular effort with straining, or during defecation or micturition the intrapulmonary pressure becomes raised by from 10 to 40 mm. Hg. If the free flow of air into and out of the lungs is hindered as a result of some diseased condition the intrapulmonary pressures will be increased beyond the normal range.

THE PLEURAL CAVITIES. (The lungs are invested by the visceral layer of the pleural membrane. The membrane is reflected from the root of each lung on to the inner aspect of the walls of the chest and upper surface of the diaphragm—this is the parietal layer of the pleura.) The two layers thus form a closed membranous sac on each side of the chest. The potential space enclosed by the pleural membranes is spoken of as the pleural cavity. In health *no actual space exists; the two membranes are in apposition* except for a thin film of fluid which serves as a lubricant to allow the surfaces to glide over one another during the respiratory movements. This potential cavity may, however, as the result of disease become an actual one. Serous fluid (hydrothorax), pus (pyothorax or empyema), blood (hemothorax) or air (pneumothorax) may collect and separate the two layers. (Between the two pleural compartments lies the *mediastinum*, a space which is subdivided by the heart with its pericardial investment into an anterior and a posterior part—the *anterior* and *posterior mediastina*.)

A simple puncture of the pleural cavity (thoracentesis) is sometimes followed immediately by fainting or collapse of the subject and may prove fatal. This so-called pleural shock has been attributed to e.g. air embolism but is most likely due to a pleural reflex which brings about cardiac slowing and a fall in blood pressure, being in this respect similar in character to the carotid sinus reflex (p. 241).

² As a result of the obstruction to breathing offered by the apparatus, these values are somewhat greater than actually exist during normal breathing.

INTRAPLEURAL (INTRATHORACIC) PRESSURES.

It has already been mentioned that the pressure on the pleural surfaces of the lungs is less than that upon their alveolar surfaces, i.e., the intrapleural pressure is subatmospheric. We must now consider the manner in which this "negative" pressure is produced. As stated above (p. 296) when the chest cavity is first expanded, the lungs are carried outwards by the inflow of air to fill the enlarged space.³ If this were all that occurred, the pressure within the lung and in the pleural cavity would be equalized and in the expanded position of the thorax after birth, as in the unexpanded state in the unborn animal, the pressure in the pleural cavity would not be subatmospheric. (The expansion of the thorax, however, and the consequent inflation of the lungs puts the pulmonary tissue upon the stretch.) In other words, the closed thoracic box, as a result of the first breath, becomes too large for the lungs to fill by a simple unfolding and distention of the walls of the air spaces. (The elastic tissue of the bronchial tree, blood vessels and of the air sacs themselves is put under stress and is constantly pulling against the stretching force.) This pull or recoil of the elastic lung amounts, in the adult when the chest is about midway between inspiration and expiration, to a pressure of from -4 to -5 mm. of mercury. The existence of such a pressure can be demonstrated indirectly by connecting a manometer with the trachea of a dead subject and puncturing the chest wall. Thus the negative pressure in the pleural cavity is abolished and the lungs are permitted to recoil, i.e., to collapse. Air is expelled from the alveoli and the manometer registers a pressure of $+4$ mm. Hg. This represents the pull which had been exerted before the puncture was made and is just equal in amount to the negative (suction) pressure in the pleural cavity. In the new-born the lungs fill the thoracic cavity with comparatively little stretching. The distention of the lungs increases, however, in later years since the thoracic cage grows more rapidly than the lungs; the elastic pull in consequence also increases and with it the intrapleural negative pressure. If, in the foregoing experiment, the lungs are distended maximally before the thoracic puncture is made, i.e., if they are fully stretched, then the pulmonary recoil causes a rise of 30 mm. Hg or so in the manometer column. The intrapleural pressure may be demonstrated

³ Some investigators believe that the normal lung is expanded in large part by "hydraulic traction" exerted on the visceral layer of the pleura by the parietal pleura and thoracic walls when these move outwards in inspiration.

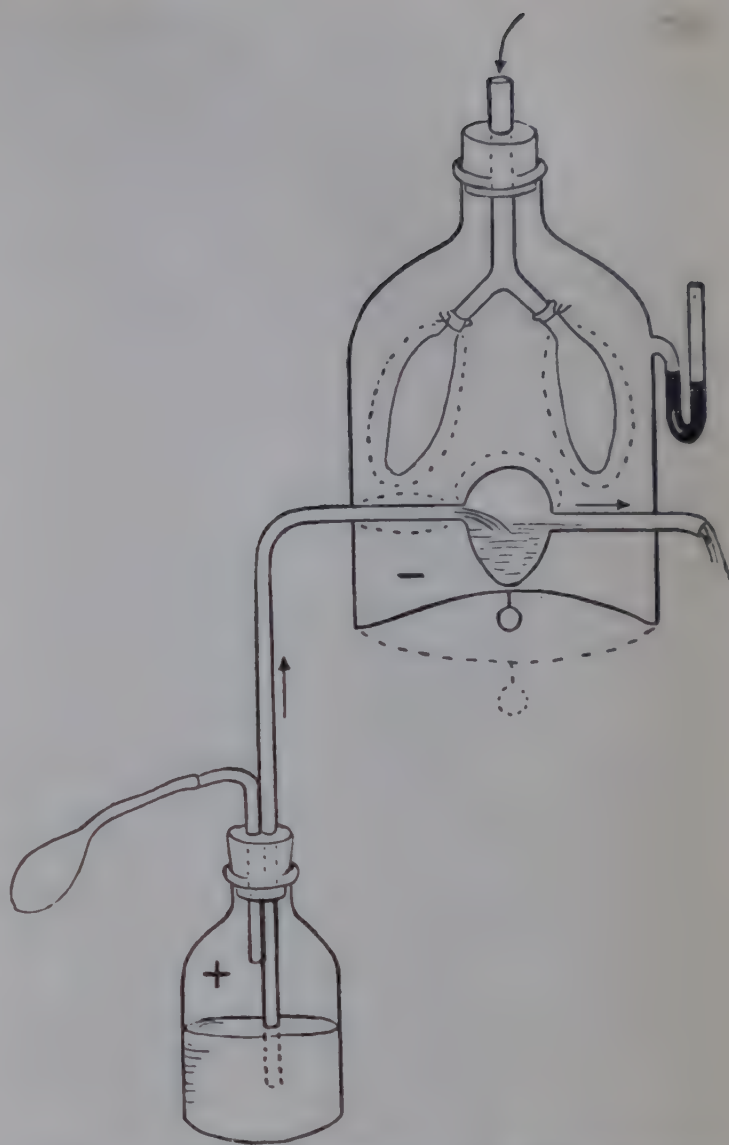


FIG. 131. Model to illustrate the manner by which changes in thoracic capacity cause corresponding changes in the volume of air in the lungs and affect the return of blood to the heart. The large glass chamber represents the thorax; it is hermetically sealed and has a flexible bottom or diaphragm. The Y-tube, which is in communication with the atmosphere, represents the trachea and bronchi; the lungs are represented by the attached balloons composed of thin rubber. The pressure within the chamber, i.e., surrounding the balloons, is subatmospheric to start with; the balloons are therefore partially expanded. When the diaphragm is drawn down (as indicated by the dotted lines) the pressure within the chamber is further reduced. The rubber balloons are distended to a corresponding extent by atmospheric air entering through the Y-tube. As the diaphragm is allowed to rise again, the "negative" pressure within the chamber returns to its previous value and the elastic balloons recoil to their original dimensions.

The bottle shown in the lower left-hand part of the drawing contains fluid upon which pressure can be exerted to cause a steady flow up the tubing into the small oval chamber within the larger one. The oval chamber may be taken to represent the heart; the tubing connecting it with the pressure bottle represents the large veins, and the tubing leading from its right side the arteries. If the tubing on the left, as well as the upper part of the oval chamber (which corresponds to the auricles) be composed of some thin resilient material, then during the inspiratory reduction in intrathoracic pressure they will undergo expansion (dotted lines). A greater body of fluid will in consequence be transferred from the bottle to the small chamber representing the heart (see p. 138).

The manometer inserted into the wall of the large chamber registers the pressure changes (indicated by dotted lines) occurring during the descent and ascent of the flexible diaphragm.

directly by plunging a cannula connected with a manometer into the pleural cavity in such a way as to prevent leakage between it and the margins of the puncture. The manometer registers a negative pressure equivalent in amount to the positive pressure recorded in the previous experiment. In other words, the mercury is "sucked" toward the pleural cavity until the pressure within the latter just equalizes that of the atmosphere.

The intrapleural pressure (and the pressure throughout the thoracic cavity generally) is always subatmospheric under ordinary circumstances,⁴ and even after death. (This "negative" pressure is increased during inspiration—since then the distention of the elastic lungs is greater—and reduced during expiration.) During the former phase of quiet respiration (human) it amounts to about -6 mm. Hg, during an ordinary expiration it is about -2.5 mm. Hg. In the midposition as stated above it is about -4.5 mm. Hg. When the movements are forced it may be very greatly increased or diminished in the respective respiratory phase. During a strong inspiratory effort with the closed glottis it may amount to -40 mm. Hg and in forced expiration under the same circumstances it is abolished and a positive pressure of 50 mm. Hg or so substituted. These changes in intrathoracic pressure exert an influence upon other thoracic structures. An increase in the "negative" pressure causes the thin-walled veins and auricles to expand and fill with blood drawn from extrathoracic regions (fig. 131). On the other hand, in forced expiration against the closed air passages the thoracic walls press powerfully upon the air-filled lungs. The rise in pressure which results is transmitted to structures lying in the mediastinum. Blood is thus expelled from the large intrathoracic veins and auricles into the veins of the abdomen and neck.

THE RESPIRATORY MOVEMENTS

What has been said in the foregoing paragraphs should have made it clear that the flow of air into and from the lungs depends entirely upon changes in the capacity of the thoracic cavity. The lungs play a purely passive rôle. The air is not drawn in and expelled by active dilatation and contraction of the pulmonary passages, as was the belief at one time. Air is drawn in or forced out strictly

in accordance with the pressure differences between the atmosphere and the lung air caused by the expansion or contraction of the thoracic boundaries, i.e., as air is drawn into and expelled from a bellows. The principles are well illustrated by the model shown in figure 131. We will now consider how these changes are brought about.

The respiratory movements of an adult person occur normally at the rate of from 16 to 18 double excursions (inspiration and expiration) per minute. In the new-born infant during quiet breathing the rate is between 30 and 40 per minute.

(During inspiration the thoracic cavity is enlarged in all diameters, vertical, anteroposterior and transverse.) The enlargement, however, is not equal in all directions (p. 300). (The upper part of the thorax increases much less in capacity than does the lower; and since the position of the spinal column remains relatively fixed the increase in the anteroposterior diameter of the thorax is due mainly to an expansion forwards. The increase in the vertical diameter is due, not to an upward expansion of the chest cavity but to the downward elongation resulting from the descent of the diaphragm.)

Unequal enlargement of the thoracic box entails unequal expansion of the lungs. The lung is not distended equally from a center as in the inflation of an elastic-walled globe. Keith distinguishes (three zones in the expanding lung.

(a) A non-expansile *root zone* containing the bronchus, pulmonary vessels and lymphatics and their main divisions.

(b) An *intermediate zone* in which the vascular and bronchial branches radiate outwards toward the lung surface. Between these rays lies expansile pulmonary tissue. This zone therefore consists of tissue of varying degrees of expansibility, that lying near the periphery of the rays being more expansile than that situated more centrally.

(c) An *outer* or *subpleural zone* from 1 to 1½ inches deep of maximal distensibility.)

Those regions of the lung lying in relation to the relatively immobile regions of the thoracic walls, namely (a) the dorsal surface of the lung apex, (b) the posterior surfaces of the lungs in contact with the spinal column and attached segments of the ribs, and (c) the mediastinal surface lying in relation to the pericardium and other structures of the mediastinum, are expanded *indirectly*. The parts of the lung which are *directly* expanded during inspiration are those lying in contact with the freely movable boundaries of the thorax,

⁴ The intrapleural pressure may be measured in the human subject by inserting a hollow needle into the pleural cavity, injecting a small quantity (40 cc. or so) of air and connecting the needle with a water manometer and a recording system.

namely (a) the sternum and ribs and (b) the diaphragm.

It is evident that those portions of lung in contact with practically stationary regions of the thoracic walls can only be expanded indirectly, that is, when other parts of the lung move out of the way. This could not occur did the root of the lung remain fixed. As a matter of fact the lung root moves downwards, forwards and laterally during inspiration (fig. 132) and, as shown by Macklin by X-ray studies upon human subjects, the bronchial tree becomes elongated (stretched)

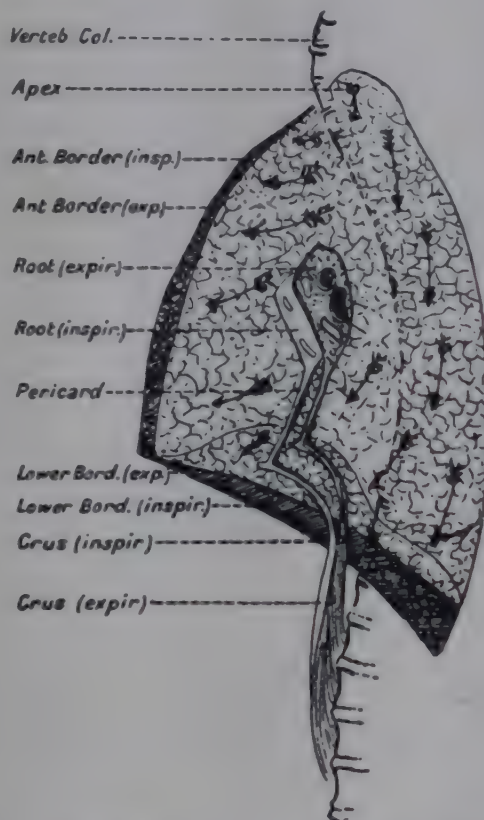


FIG. 132. Mediastinal aspect of the right lung to show the respiratory movement of the lung root. The crus of the diaphragm is also indicated, and its attachment to the root of the lung through the pericardium. The arrows indicate the direction of the inspiratory movement of the various parts of the lung. (After Keith.)

during the inspiratory phase. The trachea becomes stretched and the apex of the lung actually descends as it expands. During expiration the highly elastic bronchial tree recoils to its previous length and the lung root ascends (fig. 133). If the root of the lung were fixed, little expansion of a region such as the apex or of other regions classed as expanding indirectly could result. Nor could anything but a very moderate expansion of other regions (e.g., costosternal and diaphragmatic, etc.) occur if the bronchial tree were unable to lengthen. It is the *elongation* of the rays as described above rather than the widening of the spaces between them at their original lengths,

i.e., like the separation of the sticks of a fan, that is of importance in permitting the expansion of the intervening pulmonary tissue.

The effect of the enlargement of the thorax is exerted first and to the greatest extent upon the lung tissue in relation to the movable parts of the chest walls. The inspiratory decrease of intrapleural pressure in the diaphragmatic regions of the

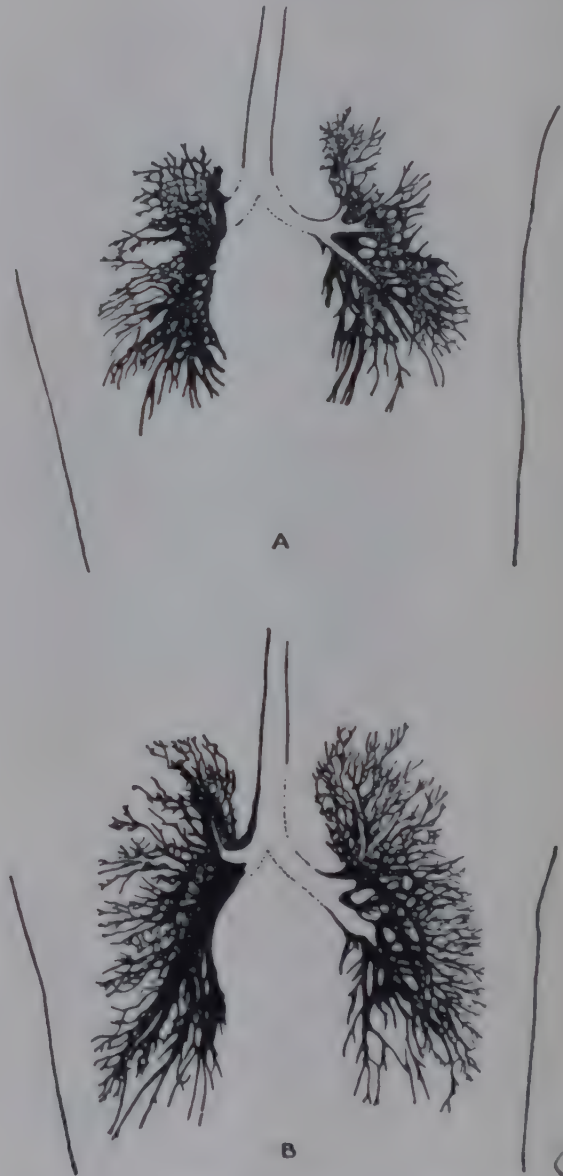


FIG. 133. X-ray photographs (retouched) of the bronchial tree of a young woman: A, in full expiration; B, in full inspiration. (After Macklin.)

thorax is considerably greater than that in the region of the apex or in other parts of the lung which are expanded indirectly. As a result of the greater negative pressure in the lower part of the thorax a horizontal groove is sometimes developed here (Harrison's sulcus) when the framework, as in rickets, is soft and yielding. The restricted expansion of the air sacs of the apex and other regions of the lung which are expanded indirectly has been held responsible for their being so commonly the primary site of tuberculous infection.

THE ENLARGEMENT OF THE THORACIC CAVITY DURING INSPIRATION

This is effected, according to Keith, by four distinct mechanisms which consist of the movements of:

(a) The *thoracic lid* or *operculum* (1st rib and manubrium sterni).

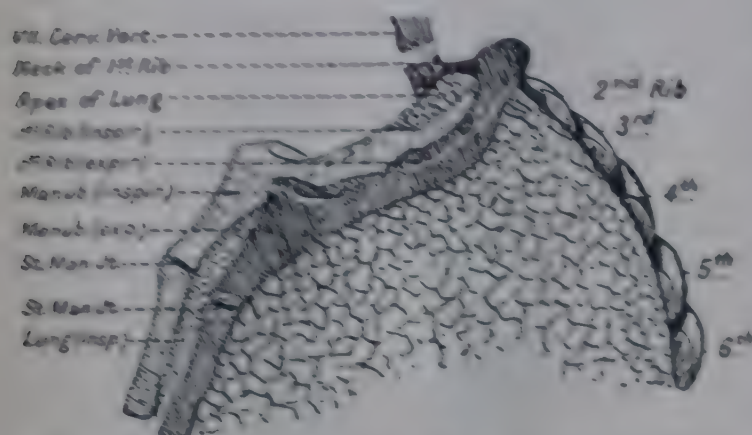


FIG. 134. Diagram to show the respiratory movements of the first pair of ribs and manubrium sterni, and the effect of these movements on the expansion of the apex of the lung. (After Keith.)

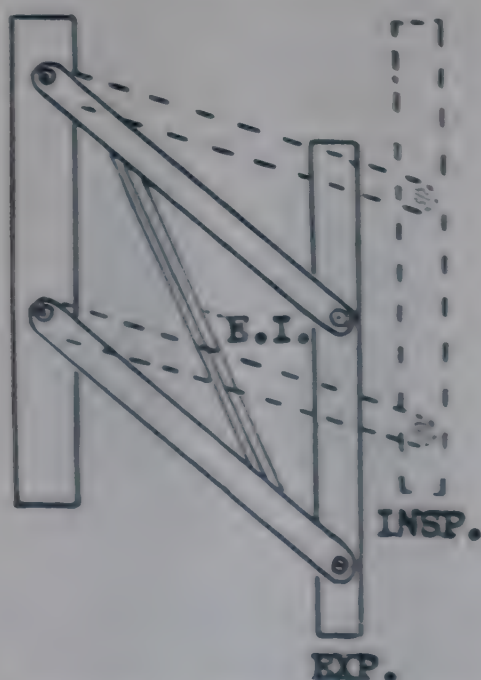


FIG. 135. Diagram to illustrate the action of the external intercostal muscles (E.I.) during inspiration; EXP., expiration; INSP., inspiration.

(b) The *upper costal series* (2nd to 5th ribs inclusive).

(c) The *lower costal series* (6th to 10th ribs inclusive) and the *diaphragm*.

(d) The *floating rib series* and the *muscles* of the abdominal wall.

(a) *The thoracic lid or operculum*

The thoracic lid or operculum is formed by the first pair of ribs and the manubrium sterni. It is

jointed behind to the spinal column and in front to the sternum by the manubrio-sternal joint. During the elevation of the thorax in inspiration the thoracic lid moves as a single piece upon the body of the sternum, assuming a more horizontal position (by from 1° to 16°). That is, the manubrium is pushed upward and forward (fig. 134). Thus, the upper part of the thorax is increased in its anteroposterior diameter. The anterior portion of the lung apex is directly expanded to some extent by this mechanism. The extent of the movement of the thoracic lid varies considerably

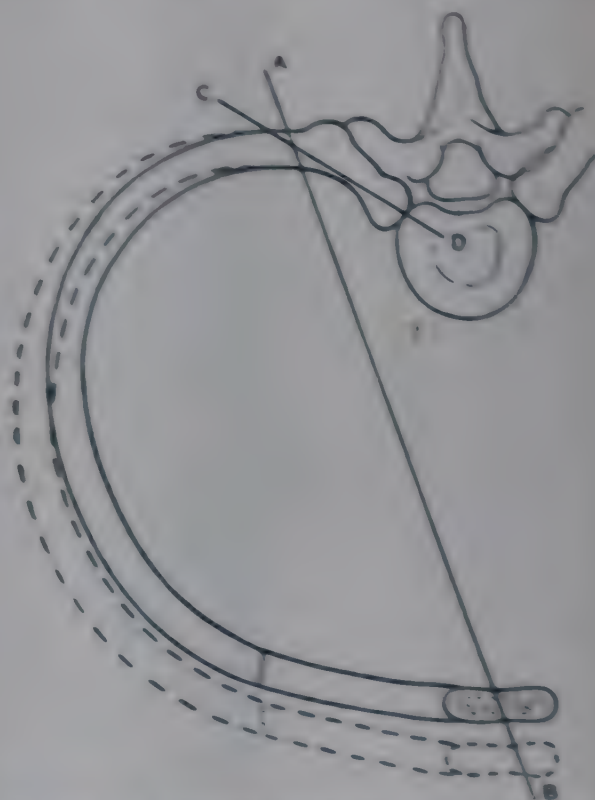


FIG. 136. A diagram showing the axis of movement (AB and CD) of the ribs from the 2nd to the 6th. The ribs from the 7th to the 10th also make a movement around an antero-posterior axis but not around the axis CD. The interrupted lines indicate the position of the rib in inspiration. (After Gray.)

in different individuals and with the depth of inspiration. It is very slight in quiet breathing. The manubrio-sternal joint becomes ankylosed in later life but rarely before the 60th year.

(b) *The upper costal series*

The 2nd, 3rd, 4th, 5th and 6th ribs slope obliquely from behind downwards and forwards. Each rib is longer, its direction more oblique and it makes a fuller sweep outwards than its neighbor immediately above. During inspiration these ribs (with the exception of the 2nd) assume a more horizontal position, their anterior portions moving upward and forward. That is, each rib rotates around an oblique horizontal axis parallel to its neck (fig. 136CD). The sternum is thrust for

ward and upward, executing a movement of the manubrio-sternal joint. These movements increase the anteroposterior diameter of the thorax. The elevation of the ribs is effected by the external intercostal muscles. The muscle fibers pass obliquely downwards and forwards from the lower border of one rib to the upper border of the rib below. When the muscle contracts it exerts a pull upon these attachments which tends to depress the upper rib of the pair and to raise the lower.

receive impulses alternately along the intercostal nerves.

The strongly bowed mid-portion of the body of each rib from the 2nd to the 6th also becomes elevated, in relation to its two ends, rotating around an oblique anteroposterior axis. This movement which is compared to the raising of a bucket-handle to a more horizontal position increases the transverse thoracic diameter (fig. 136AB).

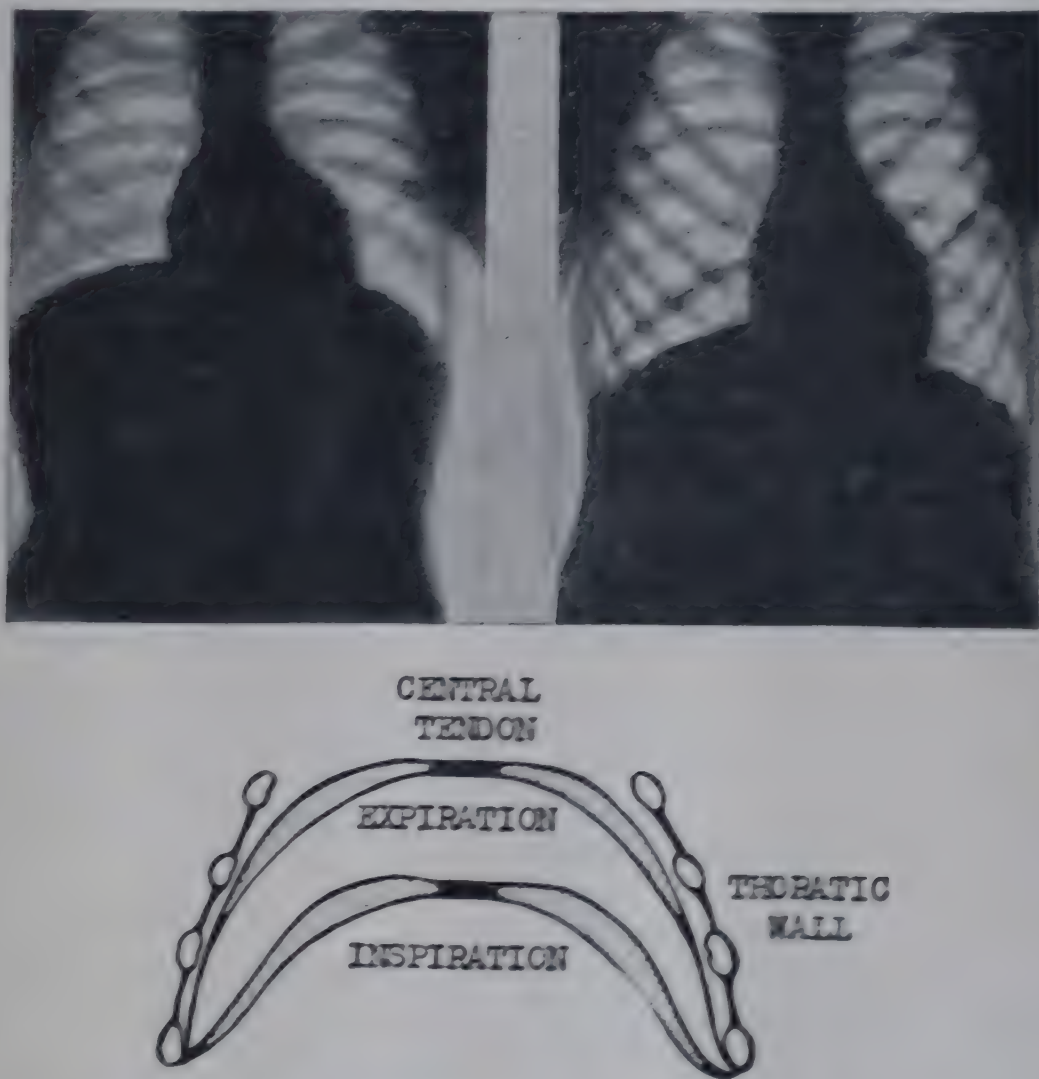


FIG. 137. Upper, radiogram showing the position of the diaphragm during expiration and inspiration. Note the effect upon the position and shape of the heart. (After Norris and Landis.) Lower, diagram showing the expiratory and inspiratory positions of the diaphragm.

The first rib, however, acts through the contraction of the scalene muscles, as a fixed point above, so that contraction of the external intercostals can only result in an elevation of the ribs. Owing also to the obliquity of the fibers which are attached below to the anterior end of the long arm of a lever and above to the posterior end of the long arm, a distinct mechanical advantage is given to the upward movement (fig. 135). The internal intercostal muscles are, in the cat at any rate, as shown by Bronk and Ferguson, expiratory in function. The internal and external intercostals

(c) The lower costal series and the diaphragm

The ribs from the 7th to the 10th also swing outwards and upwards (bucket-handle movement) during inspiration, rotating around an oblique antero-posterior axis which passes through the mid-line in front and the rib necks behind. The subcostal angle is widened by this movement and the transverse diameter of the lower part of the thorax increased; the antero-posterior diameter is slightly reduced.

The diaphragm is the chief muscle of respiration, its movements being responsible during deep

breathing for 60 per cent of the total amount of air breathed. It consists of a musculo-tendinous sheet arched toward the thoracic cavity. The tendinous portion is centrally placed (central tendon) and attached to the pericardium. The muscular tissue is placed circumferentially. (The diaphragm consists of two parts which differ from one another in their actions.

(a) The *costosternal* part arises from the back of the xiphoid and the cartilages and adjacent portions of the six lower pairs of ribs. It is attached to the anterior edge of the central tendon.

(b) The *lumbar* or *crural* part arises from the fibrous arches over the quadratus lumborum and psoas muscles and by two fleshy bundles (the crura of the diaphragm) from the bodies of the upper lumbar vertebrae. The fibers so originating are inserted into the posterior margin of the central tendon.

ACTION OF THE DIAPHRAGM. (The diaphragm descends during inspiration and ascends during expiration. In full expiration its upper limit lies at a level situated between the costal cartilages of the 4th and 5th ribs.) In quiet breathing the range of its movement is about 1.2 cm. and in forced breathing about 3.0 cm. The total diaphragmatic surface is about 270 sq. cm. A descent of 1.0 cm. therefore (assuming that all regions descend practically to the same extent) will increase the thoracic capacity by 270 cu. cm. and cause a corresponding volume of air to enter the lungs.

As the diaphragm descends its domed shape alters very little; it may be seen by means of the fluoroscope to move up and down like a piston (fig. 137). At the end of expiration a considerable proportion of the diaphragmatic surface is in contact with the chest wall as high as the 6th or 7th rib, but during inspiration it is "peeled off" the thoracic boundary, while the base of the lung expands to fill the space (pleural sinus). As a result of the slight indrawing of the intercostal spaces caused by this movement, a faint shadow may be seen to move down the side of the chest wall in most normal persons. This is known as Litten's sign. The *costosternal* part of the diaphragm, using the lower ribs, which through the action of the external intercostals serve as fixed points, moves downward and forward pushing the abdominal viscera before it. Thus, the capacity of the lower part of the thorax is increased. The abdominal wall distends but when, as a result of the resistance offered by the abdominal muscles, the downward movement of the viscera becomes arrested these act as a fixed point for the continu-

ing contraction of this part of the diaphragm. Its force is now spent in raising the lower ribs to which it is attached; through this action the sternum is thrust forward and upward. The *spinal* or *crural* part in its descent acts solely in increasing the vertical diameter of the thorax.

The excursions of the diaphragm and consequently its mid-position are influenced by (a) the upward pull of the subatmospheric intra-thoracic pressure, and (b) the abdominal viscera. In the standing position the weight of the latter exerts a downward pull and so aids the descent of the diaphragm but hinders its ascent; the mean or mid-position of the diaphragm is therefore taken up at a lower level than in recumbency when the viscera exert an upward pressure. (c) The abdominal muscles: these, when lax and the body in the standing position, allow the viscera to subside to a lower level and so to increase the downward pull upon the diaphragm. In persons with extremely weak abdominal muscles, such as subjects of visceroptosis, the downward pull upon the diaphragm greatly interferes with its movements. The breathing is then largely costal.

(d) *The floating ribs (11th and 12th) and the abdominal muscles*

Functionally the floating ribs must be considered with the abdominal muscles which are the antagonists of the diaphragm. The recti and oblique muscles relax as the diaphragm descends; they contract with its ascent.

EXPIRATION

(Expiration is to a large extent a passive movement; in quiet breathing it is probably entirely so. That is, the contraction of the inspiratory muscles ceases; the thoracic framework tends through its own weight to resume its former position, the elastic lungs recoil and the relaxed diaphragm is drawn upwards toward the thoracic cavity by the "negative" intrathoracic pressure which is greatest at the end of inspiration. There is, however, also a definitely active element in a forced expiratory movement. As mentioned above, the abdominal muscles contract and by pressing upon the viscera aid the ascent of the diaphragm, i.e., the diaphragm is "pushed" up by the increased intra-abdominal pressure resulting from the contraction of the abdominal muscles, as well as "sucked" up by the subatmospheric pressure within the thorax.

During forced expiration the internal intercostals whose fibers like those of the external intercostals course obliquely but in the opposite direction

downwards and backwards) contract and so aid in the depression of the ribs. The restoration of the thorax to its previous diameters is, of course, accompanied by a corresponding reduction in the capacity of the lungs and the expulsion of air from its air spaces.

MOVEMENTS OF THE BRONCHIAL TREE DURING RESPIRATION. In addition to the inspiratory elongation of the bronchial tree mentioned above, the bronchioles and smaller bronchi dilate during inspiration and constrict during expiration. The rhythmical bronchial movements appear, from the studies of Ellis and of Nicholson, to be purely passive in nature and not integrated through reflex mechanisms with inflation and deflation of the lungs. The bronchioles also exhibit a peristaltic movement which can be detected by X-ray photographs of the bronchioles after the injection of lipiodol⁵ or other material which is opaque to the X-ray. It is not thought that the peristaltic movement plays any part in the movement of air, but it appears to assist in the movement of foreign material towards the large air tubes. This bronchiolar peristalsis is said to be increased in lung abscess and diminished in bronchiectasis. It is decreased by morphine.

PULMONIC ALVEOLAR VENTS. The existence of certain pores in the alveoli (pores of Kohn) have long been recognized, but the difficulty of being certain that they are not artefacts produced by the method of preparing the sections has prevented their wide acceptance as normal structures. Quite recently, however, Macklin has been able to demonstrate the presence of such vents in thick sections prepared from the lungs of many species including man. Examination of the sections justifies the belief that they are normal communications between the alveoli. While the function of the vents is not as yet completely understood, it appears probable that they play a significant part in the equalization of pressures in groups of the alveoli, particularly perhaps during forced inspiration. The vents are opened wide during inspiration and may be entirely closed in expiration. The rôle of these passages in the spread of infection will doubtless receive serious consideration.

COLLATERAL RESPIRATION. This phenomenon (Van Allen, Lindskog and Richter) depends on the fact that the lobular divisions of the bronchial tree of any one pulmonary lobe are interconnected. Air may pass from one alveolus to an adjoining one presumably through the alveolar vents but possibly also by rapid diffusion. This communication may be demonstrated when a bronchus supplying one lobule is obstructed, for it is then found that the alveoli of the obstructed

lobule may be well ventilated for prolonged periods. Collateral respiration is prevented by inflammatory exudates or secretions or in circumstances in which the alveolar walls are not adequately distended. In this latter case the vents may not be open. In species in which the interlobular septa are complete as in man there is no provision for collateral respiration between different lobules. Experimental evidence has been obtained which indicates that atelectasis of a lobule does not develop after obstruction of its bronchus. Conversely, re-aeration of an atelectatic lobule may take place by this collateral route. It would thus appear that considerable anatomical and physiological evidence has been obtained for a peripheral mechanism which has as its objective the adequate and uniform but not excessive distension of the pulmonary alveoli.

EXPULSION OF FOREIGN MATERIAL—THE ACT OF COUGHING. There are three mechanisms for the expulsion of foreign material. First, the action of the cilia, p. 293; second, the peristaltic motion in the bronchioles; and third, the cough reflex. The peristaltic movement has been referred to above. The cough reflex is most commonly initiated by the stimulation of afferent nerve endings in the region of the tracheal bifurcation, the most sensitive area, or in the laryngeal mucosa. It may also be initiated from the excitation of vagal afferents in the lungs, or from nerve endings in the pleura. Ear disease, through the stimulation of terminals of the auricular branch of the vagus (Arnold's nerve), may also cause coughing. The act itself consists of a short inspiration followed immediately by closure of the glottis and a forcible expiratory effort. A considerable degree of pressure is thereby developed within the lung. The glottis then opens suddenly and offending material is moved a variable distance along the air passage. If it reaches an insensitive area the coughing ceases. During the subsequent inspiration the irritating particle, if not large enough to seriously obstruct the air passage, remains during the subsequent inspiration in its new position, from which it is carried forward again during succeeding expulsive efforts until it is swept away from sensitive areas.

Hiccup or singultus is a spasmodic and purposeless contraction of the diaphragm which results from many causes or may occur without known cause; it occurs rarely in epidemic form. It is usually reflex in nature being initiated by some abnormal stimulation of the afferent nerve terminals in the diaphragm. The fibers of the phrenic nerve constitute the efferent limb of the reflex. In some instances, hiccup may be due to stimulation of the respiratory center itself by some agent

⁵ A preparation of iodized oil.

in the blood. Hiccup following abdominal operations may be most intractable and endanger the life of the patient. The inhalation of an air mixture containing 6 or 7 per cent of carbon dioxide (or simply breathing and rebreathing from a bag for a number of respirations) has been reported to be a valuable means of terminating an attack.

Artificial Respiration

Schafer's prone pressure method is the best known and most widely practised means of artificially ventilating the lungs when spontaneous respiration has failed. It has the advantage that it requires no special equipment and can be undertaken by one person. The operator kneels astride the subject stretched prone beneath him and with the palms of his hands upon the subject's lower ribs leans forward and exerts gentle but

expand the chest. The arms are returned to the ground during the expiratory phase. In the rocking method the inspiratory and expiratory movements of the diaphragm are brought about by the weight of the abdominal viscera. The subject is placed prone upon a stretcher which is then rocked on a trestle around a transverse axis. The tilt of the body both in the head-down and feet-down positions is from 45 to 50 degrees. Ten double movements are made per minute. This method is also believed to encourage the circulation of blood through the coronary and cerebral vessels and thus to sustain the vitality of the myocardium and nervous centers.

During the last few years several methods have been developed for the long continued application of artificial respiration by various mechanical processes. This work was begun by Thunberg

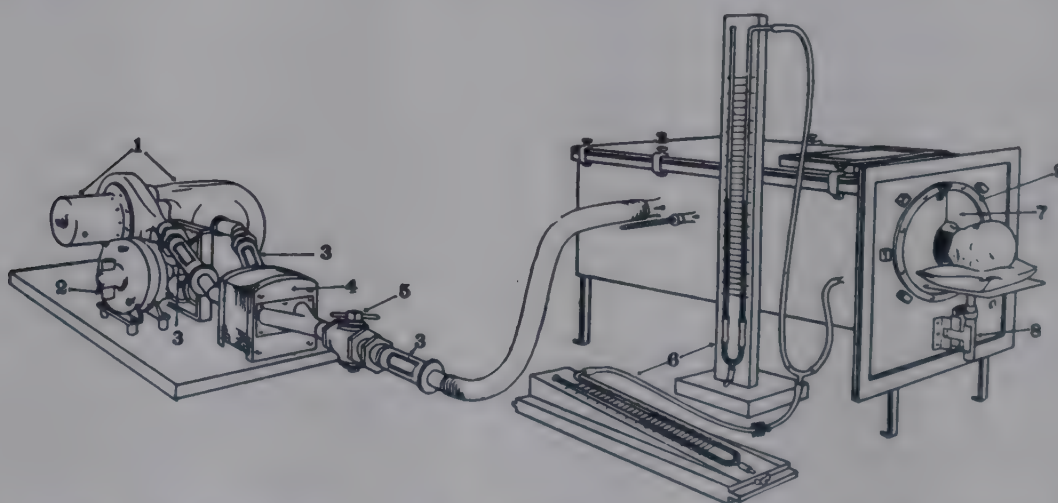


FIG. 138. The Drinker respirator. 1, pumps; 2, motor; 3, vents; 4, alternate; 5, valves; 6, manometers; 7, external shutters; 8, adjustment for head rest; 9, adjustable ring to hold collar in place. (After Shaw and Drinker, *Jour. Clin. Investig.* 1930/8/33.)

firm pressure for 2 seconds. He then straightens up and releases the pressure for 2 seconds. These alternating movements are repeated at the rate of normal respiration. The downward and forward movement compresses the thorax and pushes the diaphragm upward, thus expelling air from the lungs. The recoil of the thorax to the resting position follows the release of the pressure, and thus induces artificial inspiration. It has been found, however, from experiment that this method does not provide sufficient pulmonary ventilation in an animal whose respiratory muscles have been paralyzed by curare (Meltzer). Much more adequate aeration of the lungs is claimed for the Neilson-Schafer (Drinker) method and for Eve's rocking method. In the former procedure the extended arms of the subject are raised above his head by a second operator during the inspiratory phase of "Schafer respiration." This helps to

in Lund who devised an apparatus called the barospirator. The subject was placed inside a metal chamber in which the pressure was raised and lowered rhythmically by means of the stroke of a very large piston. The interchange of air within the lungs was caused by a rise and fall of pressure of the air in the external atmosphere. This apparatus was effective and a model was built large enough to accommodate patient, nurse and doctor. All three were ventilated without movement of the chest. A certain amount of discomfort was experienced in this cabinet due to the change in pressure on the two sides of the eardrum during the increase and decrease of air pressure. A more generally applicable model was produced by Drinker at Harvard. In this type the patient's head remains outside the cabinet (fig. 138). The chest is expanded by reducing the pressure within the cabinet and as the pressure is

raised again, the natural elasticity of the lung causes expiration. Forced expiration, however, may be produced by raising the pressure above atmospheric. Patients have been adequately ventilated with this apparatus for many months. Some difficulty is occasionally encountered in the regulation of the rate and depth of respiration, but by determining the oxygen saturation of the arterial blood or watching for signs of cyanosis an observer can usually regulate the ventilation quite satisfactorily.

Two other types of apparatus should be mentioned; (1) the jacket model of Sahlin which operates like the Drinker machine but is applied only to the chest, and (2) the Bragg-Paul pulsator which consists of a hollow elastic bandage placed around the chest. The bandage, when inflated by an electrically driven bellows, compresses the chest, which returns to the mid-position by virtue of its own elasticity during the intervals between the compressions.

The object of artificial respiration is not only to aerate the lungs but also to stimulate the respiratory center. Due largely to the insistence of Yandell Henderson, carbon dioxide is now added, whenever possible, to the respired air which should contain from 40 to 50 per cent of oxygen. The high carbon dioxide tension combined with the rhythmical inflation and deflation of the lungs, which presumably cause the discharge of afferent impulses, encourage the return of spontaneous breathing.

PNEUMOTHORAX

Air may enter the pleural cavity through a penetrating wound of the chest (*open pneumothorax*), as a result of the rupture of an emphysematous vesicle on the surface of the lung or from the extension through the pleura of a lesion of the pulmonary tissue (e.g., tuberculous) or of some other air-containing organ such as the esophagus or stomach. When the intrapleural space contains air but communication with the atmosphere has become occluded the pneumothorax is said to be *closed*.

OPEN PNEUMOTHORAX

If the opening through the thoracic wall were large and the mediastinum acted as a more or less rigid partition the pleural cavity of the affected side could be considered quite separate from that of the sound side. The lung on the open side would exhibit its elastic properties and recoil; the reserve and residual airs (p. 308) would be expelled and the lung would be in the collapsed state. The

opposite lung would be unaffected. Actually, the mediastinum, as a rule, offers little resistance, so the two pleural cavities, though anatomically separate, act so far as the distribution of pressure is concerned, almost as if they were a single cavity. Consequently when an opening exists in the thoracic wall the yielding mediastinum with its contents—heart and great vessels—moves toward the sound side and the increased intrapleural pressure is transmitted to that side. The negative pressure on both sides of the chest is therefore reduced and both lungs tend to collapse, but, the pressure on the sound side is always altered less than the pressure on the side of the opening. Graham and his associates found in experiments upon the human cadaver and upon the living dog that an air pressure of +10 cm. of water created in one pleural cavity, caused the pressure in the opposite pleural cavity to rise to between +7 and +8 cm. With the introduction of higher pressure a greater difference was found between the two sides. For example, when a pressure of 48 cm. of water was created in one pleural cavity the pressure on the opposite side was less than 21 cm.

Other things being equal the size of the opening in the chest determines the extent to which the negative pressure becomes reduced. If the chest were immobile and the mediastinum quite unresisting this factor would exert no influence upon the pressure ultimately attained within the thorax. The pressure would finally become atmospheric throughout and complete collapse of both lungs would result. But in the living body the response to pneumothorax is to deepen the respirations. That is, the thorax enlarges and the lungs expand to a greater degree to maintain the negative pressure despite the communication between the chest cavity and the atmosphere. It therefore becomes a matter of competition between the amount of air entering the lungs through the trachea and that entering through the opening in the chest during inspiration. The chest may be compared to a bellows with a hole in its wall; when the bellows is opened (inspiration) the volume of air entering through the leak and that through the nozzle (which is analogous to the trachea) will depend upon the sizes of the respective openings. From this it will be realized that with quite a small opening an intrapleural pressure of practically normal value could be maintained. Even with a very large opening—one exceeding in extent by several inches the cross area of the trachea—though the intrapleural pressure could not be maintained at its normal value and partial collapse of the

lungs would result, nevertheless, a normal volume of air could be drawn in during inspiration. The reason for this is, of course, that the amount of air required for ordinary existence—tidal air—is only a small fraction of the vital capacity. In other words a partially collapsed lung is adequate for ordinary needs. When, however, the opening is so large that the thorax, even when maximally enlarged, cannot expand the lung sufficiently to maintain the tidal air at its normal value, dyspnea and cyanosis will result and the patient will die. It also follows that a patient whose vital capacity is already reduced by disease cannot survive with an opening as large as that which can be tolerated by a person possessing a larger vital capacity. As a result of the work of Graham and his associates the following summary may be made.



FIG. 130. Bronchiectasis. X-ray photograph after injection of bronchial tree with lipiodol. (After Moll, retouched.)

(a) Both lungs are affected in a pneumothorax. If the opening is small or if in a closed pneumothorax the pressure is low, the effect upon the two lungs is nearly equal.

(b) A bilateral open pneumothorax is not fatal unless the openings are large.

(c) The size of the opening compatible with life bears a relation to the vital capacity of the subject. Any pneumothorax, unless the opening is very small, would be fatal to a person who before the pneumothorax occurred had possessed a vital capacity little greater than his tidal air. It is therefore possible to perform an intrathoracic operation upon a subject possessing a high vital capacity without distending the lungs by the delivery of air under pressure through the trachea.

(d) The reduction in the intrathoracic "negative" pressure caused by a pneumothorax tends to impede the filling of the right heart and to produce stasis in the venous system (p. 138).

(e) Open pneumothorax increases the heat loss of the body. In dogs the body temperature usually falls 2°C. half an hour after an opening has been made in the chest. After closure the temperature rises again and within an hour has nearly reached the normal level.

When the mediastinum has been rendered solid and resistant by previous disease some of the foregoing statements obviously will not apply. All if the pleural surfaces on the side of the opening are adherent and so hold the lung out against the thoracic wall a pneumothorax will not result. If, as a result of such adhesions the pneumothorax is limited in extent, only a part of the lung is affected.

COLLAPSE OF THE LUNG, ARTIFICIALLY INDUCED. Pulmonary collapse is induced as a therapeutic measure in certain pulmonary lesions, especially tuberculosis, in which the disease is mainly confined to one lung. The operations employed are (a) *pneumothorax*, (b) *phrenic avulsion*, (c) *thoracoplasty*. The aim is to render lung functionless and so to place it at rest. Healing is thereby promoted. Benefits also result from obliteration of the vessels of the diseased lung. Blood is diverted from the poorly aerated tissue to healthy lung, whose capillary bed becomes enlarged for the accommodation of the blood. Anoxia and other effects are thereby relieved (see p. 364). (a) *Pneumothorax*. The pneumothorax is of the closed type, air is introduced into the pleural cavity under pressure. The injected air after a time becomes absorbed (see atelectasis, p. 370) and the operation must be repeated in order to maintain the lung in the collapsed state. This operation or phrenic avulsion (below) is employed in the comparatively early stages of pulmonary tuberculosis. (b) *Phrenic avulsion*. One or other phrenic nerve is exposed in the neck and sectioned. The lower segment is then seized with forceps and pulled until it gives way, a considerable section of the nerve being removed. The corresponding half of the diaphragm is paralyzed. The latter ascends into the thoracic cavity where it remains fixed at a high level. The capacity of that side of the thorax is reduced, the lung collapsed to a corresponding degree. A section of the phrenic in the neck is ineffective as a means of paralyzing the diaphragm since fibers of the 5th cervical nerve (accessory phrenic) join the main trunk of the nerve within the thorax.* (c) *Paravertebral thoracoplasty*. This operation is performed in advanced cases with cavity formation and when pleurae are adherent and consequently an artificial pneumothorax is not feasible. From 1 to 6 inches

* As a matter of fact simply crushing the nerve is often resorted to in order to reduce the mobility of the affected lung for a time. Regeneration of the nerve occurs after a year or so.

the upper nine or ten ribs are removed from the back of the thorax. The chest wall thus rendered plastic contracts inwards and compresses the corresponding lung.

Pleural shock. Marked slowing of the pulse and a profound fall in blood pressure, which may lead to fatal syncope, sometimes follows puncture of the chest wall for the withdrawal of fluid or during the production of pneumothorax. The cardio-vascular reaction is apparently due to a pleural reflex since a similar effect upon heart rate and blood pressure can be induced in animals by stimulating the pleura. It is more commonly seen when the chest is punctured for the withdrawal of fluid than during the injection of air for the production of pneumothorax, a fact among others which argues against its being due to air embolism (footnote, p. 142). Injury to the visceral pleura or to the underlying layer of pulmonary tissue appears to be a factor essential for the production of this type of circulatory collapse.

BRONCHIECTASIS

This is the term applied to an abnormal dilatation of the bronchi or bronchioles. The dilatation may be localized or widespread, fusiform, irregular, beaded or uniform in distribution. The contour of the bronchial tubes is readily demonstrated by X-ray after the injection of lipiodol (fig. 139). Secretion may collect within the dilated lumen and be expectorated at intervals as large quantities of a foul-smelling sputum. This classical sign of the condition is only seen in its advanced stages. More commonly the sputum is small in amount and in the form of yellow "chunky" pieces (Warner).

Causation

Bronchiectasis is practically always secondary to some other affection of the lungs. The primary change leading to the condition is weakening of the bronchial wall as a result of infective processes. The elastic and muscular tissues are

atrophic. As we have seen (p. 303) the bronchial tree dilates during inspiration and contracts during expiration. The latter movement is, in part at least, an elastic recoil. With the gradual deterioration of the elastic tissue of the bronchial wall, the latter's resiliency becomes progressively less. The lumen of the tube does not regain its normal caliber after inspiration but remains more or less dilated. Dilatation beyond this is due to the fact that during inspiration the pressure within the bronchial lumen is greater than the pressure within the extrabronchial tissues and throughout the thoracic cavity generally. During expiration, however, the intrabronchial pressure cannot rise above the pressure in the surrounding tissue; the bronchial walls are supported. Coughing or other conditions causing a general rise in intrapleural pressure cannot, therefore, induce bronchiectasis. On the other hand conditions which increase the negative pressure within the thorax, such as the collapse of a lobe (lobar atelectasis) as a result of a bronchial occlusion or of an entire lung (massive atelectasis) (p. 370), will obviously increase the tendency to bronchiectasis. Lobar atelectases were found in 6 per cent of cases of bronchiectasis observed by Warner and Graham. Incomplete obstruction of a bronchus especially if it exerts a valve-like action, by permitting inspiration but hindering expiration, favors the development of bronchiectasis (see also p. 369). The latter is therefore not an uncommon result of the lodgment of a foreign body in a bronchus.

Fibrosis of a lung or portion of lung is considered by some as a potent cause of bronchial dilatation. It is thought that the fibrosing lung as it shrinks makes equal circumferential traction upon the bronchi or bronchioles and thus leads to their dilatation. It is probable that even in these instances previous weakening of the bronchial wall is the primary fault since bronchiectasis commonly occurs in the absence of fibrosis.

CHAPTER XXX

THE AIR OF THE LUNGS

The quantity of air drawn into and expelled from the lungs in quiet respiration is only a fraction ($\frac{1}{3}$ or so) of that which can be inhaled and exhaled during deep breathing. The air which passes in and out during ordinary respiration is spoken of as the tidal air. It amounts on an average to 500 cc. The average man after he has completed an ordinary expiration, can inhale, by making the deepest inspiration of which he is capable, about 3000 cc.¹ This is termed the *complemental air*. If, starting again from a position of rest, i.e., at the end of an ordinary expiration, a forcible expiratory effort is made, about 1000 cc. can be expelled. This is called the *supplemental air*. Since in ordinary breathing the lungs must hold this extra quantity of air which can be expelled upon demand it was called the *reserve air* by Hutchinson. The volumes of the complemental and supplemental airs, i.e., the total amount of air which can be exhaled after a maximal inspiration, is called the *vital capacity*. Thus, in round figures,

Tidal air.....	500 cc.
Complemental air (including tidal air).....	3000 cc.
Supplemental (reserve) air.....	1000 cc.
Vital capacity.....	4000 cc. ²

(see fig. 140).

Even after the most strenuous expiratory effort a large quantity of air still remains in the lungs, since collapse of the air cells cannot occur so long as the intrathoracic pressure remains negative (subatmospheric). This is termed the *residual air*. It is present in the lungs after death but is expelled in large part when the pleural cavity is opened and the pressure upon the two sides of the lung becomes equalized. The residual air amounts to from 1000 to 1500 cc. but it shows considerable individual variation.

When the lungs collapse as a result of opening the chest, the small amount of air which still remains entrapped within the air sacs and cannot

be expelled by ordinary means is known as the *minimal air*. The minimal air is responsible for the characteristic buoyancy of pulmonary tissue. The lungs of a dead animal float in water and for this reason are popularly known as the "lights." The fact is important in medico-legal practice and is applied as a test to determine whether an infant was still-born or had died after having once breathed.

Further partitions of the lung are distinguished by clinicians. Thus *total lung capacity* is the vital capacity plus the residual air, that is, the total volume of air which the lung can hold after a maximal inspiration. It amounts to about 5000 cc. The *minute volume* is the total volume of air breathed per minute, i.e., the volume of the tidal air multiplied by the number of respirations per minute.

The *functional residual air* is the amount of air remaining in the lungs at the end of a normal expiration, that is, the supplemental or reserve air plus the residual air.

THE VITAL CAPACITY (V.C.) AND ITS VARIATIONS

A relationship between certain body measurements and vital capacity has been shown by several investigators. Hutchinson, a pioneer in the field, invented the spirometer and studied the vital capacity in a large number of individuals, normal and diseased. He demonstrated the relation of vital capacity to height and weight.³

³ Dreyer investigated the vital capacity in a number of healthy individuals and demonstrated a relationship between it and "stem length" (height of body from chair in sitting position) weight, and body surface respectively.

For the average healthy person the relationship between vital capacity and weight is shown in the formula:

$$\frac{W^n}{V.C.} = K$$

When W = weight of body in grams; power n = 0.72; V.C. = vital capacity in cubic centimeters; K = a constant having a value of 0.690. The normal standard for a given weight is calculated as follows:

$$\frac{W^{0.72}}{0.690} = V.C. \text{ in cubic centimeters}$$

¹ This of course includes the tidal air. Some take the volume which can be inspired after a normal inspiration as the complemental air. It then does not include the volume of the tidal air.

² The values vary considerably between individuals. Those in the table are for a healthy adult male of average build.

The most consistent relationship, as shown by Dreyer and by West, exists between vital capacity and surface area (see table below).

A fairly close relationship between total height and vital capacity was also found, the latter expressed as cubic centimeters being 25 times the height in centimeters for men, 20 times for women and 29 times for athletes. For example, an average adult male 170 cm. tall would have a vital capacity of $(170 \times 25 =)$ 4250 cc. The surface area of the same individual assuming an average weight for his height, namely, 70 kgm., would be 1.80 square meters. Therefore his vital capacity should be $(1.80 \times 2500 =)$ 4500 cc. The difference in the results of the two methods of calcula-

sedentary work being considerably lower than those pursuing more arduous occupations. Dreyer divided his subjects into three classes A, B and C. Class A are those with the maximum vital capacities. Classes B and C have values 90 per cent and 85 per cent respectively of those of Class A. He considers a reduction of 15 per cent below the standard of the class to which the subject belongs as an almost certain indication of some abnormality. It should be mentioned that measurements of chest expansion, as by means of a tape measure may bear little relation to the vital capacity. A subject with powerful muscles can enlarge his thoracic cage to a capacity greater than his lungs are able to fill. His diaphragm

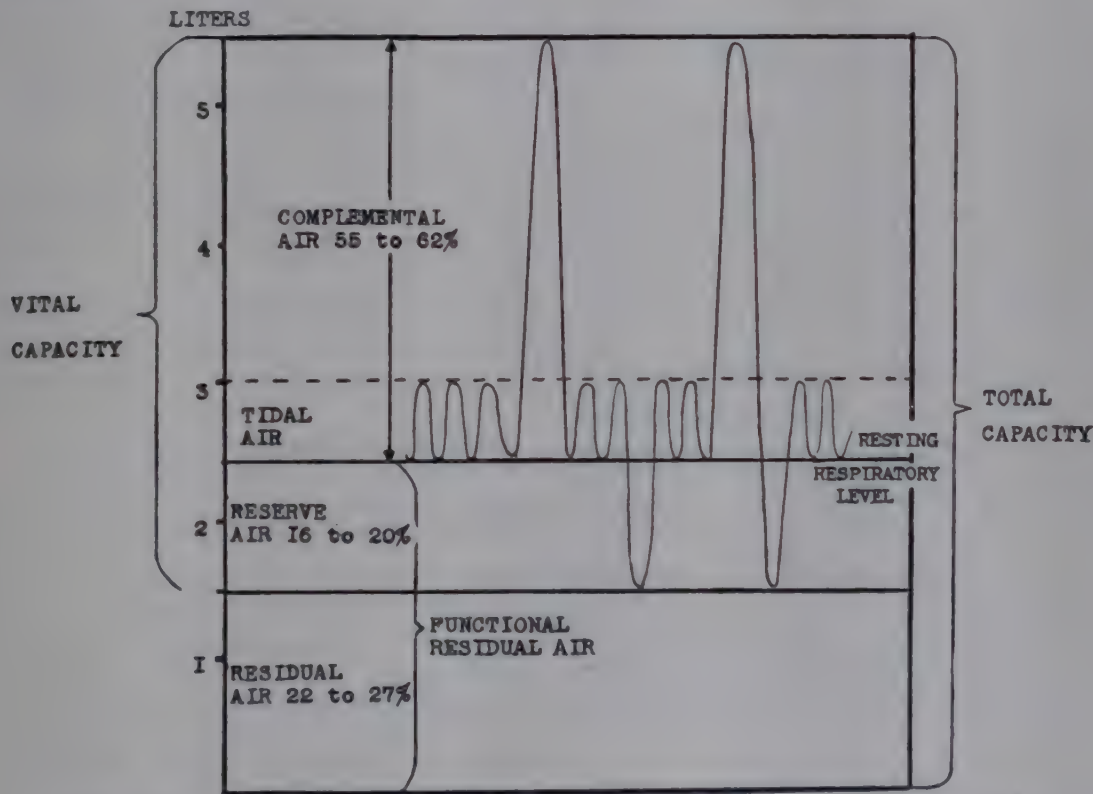


FIG. 140. Showing subdivisions of lung air. (Modified from Christie.)

tion of the normal standard is therefore around 5 per cent.

The ratios of vital capacity to height and surface area respectively, as found by West, are shown in the following table:

	Men	Women	Athletes
Vital capacity, cc. per cm. height.	25.0	20.0	29.0
Vital capacity, cc. per square meter of body surface.....	2500	2000	2800

Occupation as shown by Dreyer and others exerts a potent influence upon the vital capacity. The normal standard of persons employed in

The subject's vital capacity as directly measured by the spirometer is expressed as a percentage of the normal standard for age, sex and occupation.

instead of taking a full downward stroke is drawn upwards while the viscera are forced into the extra-thoracic space by a strong contraction of the abdominal muscles.

The vital capacity is reduced in many diseased conditions especially those involving the respiratory and vascular systems. Among these are

(a) Conditions which directly involve the lungs, e.g., pneumonia, pulmonary tuberculosis, emphysema, etc.

(b) Mechanical interference with the enlargement of the thoracic cavity, e.g., as by abdominal conditions impeding the movements of the diaphragm or abnormalities of the thoracic walls. The movements of the thoracic walls may be seriously restricted by abdominal or pleuritic pain.

(c) Intrathoracic conditions which encroach upon the space normally occupied by the lungs, e.g., pericardial or pleuritic effusions, pneumothorax, tumors, etc.

(d) Heart disease. Engorgement of the pulmonary vessels causes an encroachment upon the alveolar spaces and so reduces their capacity. Pulmonary edema involving especially the lung bases is a contributory factor in the reduction of the vital capacity in cardiac cases. Peabody found that when in heart disease the vital capacity reached 40 per cent of the normal, the subjects were almost constantly dyspneic or showed dyspnea upon the slightest exertion (p. 354).

The vital capacity, the functional residual air and the residual air and consequently the total lung capacity are reduced in the recumbent posture.

METHODS OF MEASUREMENT

It must be emphasized that any reduction of the vital capacity of an individual is of much greater significance than an apparently abnormal value encountered at the first examination. The vital capacity, the complementary air, or the reserve air can be readily measured in a simple spirometer. For the determination of residual air or the volume of the lung at any phase of respiration the modification of Humphrey Davy's dilution method described by Van Slyke and Binger is recommended. Oxygen to which a known volume of hydrogen has been added is breathed in and out from a spirometer. The carbon dioxide is absorbed by sodium hydroxide. A sample of the mixture is analysed and the ratio of N_2 to H_2 determined, since,

$$(1) \quad \frac{N_2 \text{ in sample}}{H_2 \text{ in sample}} = \frac{\text{Total volume } N_2}{\text{Total volume } H_2}$$

and (2) the total volume of H_2 being known, the total volume of N_2 in the lungs can be calculated; then in as much as nitrogen forms 79 per cent

$$\text{of the lung air, } \frac{\text{vol. } N_2}{79} \times 100 = \text{lung volume.}$$

ALVEOLAR AIR

This is the air contained in the air sacs and alveoli. Its gases come into equilibrium with those in the blood of the pulmonary capillaries. The alveolar air is being continually renewed through the to and fro effect of the respiratory movements. But since the lungs are not emptied during expiration it is quite clear that complete renewal of the air cannot be affected by a single respiration. The ventilation of the lungs occurs by the mechan-

ical mixing of the inspired air with the lung and by the slower process of diffusion. During expiration the air of the upper respiratory passage is first expelled; then follows a part of the air of the bronchial tree. At the end of expiration the air which has been in the distended alveoli, since they have been reduced in capacity, now overflows into the bronchioles and bronchi. At the next inspiration this air is swept back again into the air sacs its place being taken by fresh atmospheric air. The latter as compared with the alveolar air has a high oxygen pressure and a low pressure of carbon dioxide. Oxygen therefore diffuses from the inspired to the alveolar air and carbon dioxide passes from alveolar to inspired air. The mechanical mixing of the inspired air with the air already in the lungs occurs, chiefly, at the beginning

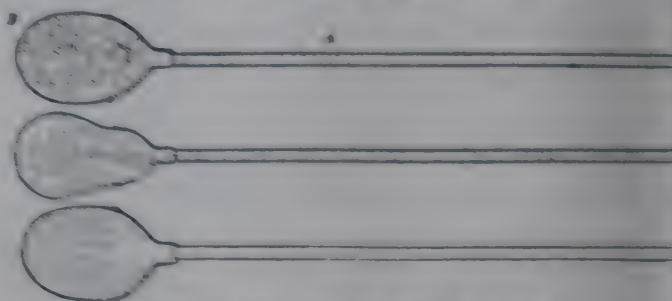


FIG. 141. Description in text.

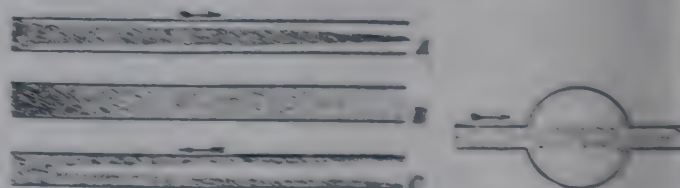


FIG. 142. A shows a 'spike' of smoke moving through a glass tube. B shows the condition when the current is suddenly stopped and mixing occurs instantaneously. C shows clear air drawn in through a glass tube, showing how a column of smoke crosses a bulb with mixing or sweeping out of the air within it. (A. Yandell Henderson and associates.)

inspiration and the end of expiration. Mixing is also brought about through the convection currents set up by the entrance of the cooler atmospheric air.

The process by which the air in the alveoli is renewed may be made clear by the illustration in figure 141. A is a glass tube to which is attached a compressible bulb B. If the bulb be filled with smoke then compressed, the smoke will not be completely expelled by a single compression. A portion only issues from the end of the tubing. The rest will be in the compressed bulb and tubing. When the bulb is released again smoke will be drawn back into the bulb and the tubing will be filled with fresh air. The smoke in the tube will be diluted through mechanical mixing and diffusion. After a series of compressions the smoke would be completely cleared away. If the air were supplied steadily with smoke through the

and rhythmical compressions and decompressions the bulb maintained at a definite rate, a certain constant dilution of the smoke would result. The smoke entering the bulb may be taken to represent the carbon dioxide passing from the blood into the alveolar spaces. Henderson and his associates have shown that when one gas displaces another from a cylindrical tube the interface between the two is not a plane surface. On the contrary, the displacing gas advances in the form of a cone or spike leaving a layer of the gas which is being displaced clinging to the tube's walls. This fact may be demonstrated by displacing air from a glass tube by a puff of smoke (fig. 142). When the current of smoke ceases mixing occurs.

Obtaining a sample of alveolar air

It is clear from the foregoing illustration that in order to obtain a sample of pure smoke as it issues from the end of the tubing all the air must be first swept out. Similarly in order to obtain pure alveolar air a forced expiration must be made and a sample collected as close as possible to the subject's mouth. This is accomplished through the use of the Haldane tube, which consists of a length of hose-pipe 1 inch in diameter and 3 feet long and provided with a mouth piece and sampling bulb as shown in figure 143. The subject after a



FIG. 143. Haldane tube and sampling bulb.

normal expiration makes a forced breath down the tube. Toward the end of this act the sampling bulb, which has been previously evacuated, is squeezed for a moment in order to permit the expired air to be drawn in, and then closed. An all glass syringe may be used instead of the sampling tube. The exact technique used in research is somewhat more complicated than that described above.

The following are the average compositions of inspired, expired and alveolar airs reduced to standard temperature and pressure (S.T.P.).

	Volumes per cent		
	Inspired (atmospheric) air	Expired air	Alveolar air
Oxygen.....	20.94	16.3	14.2
Carbon dioxide.....	0.04	4.0	5.5
Nitrogen (including argon and other inert gases).....	79.02	79.7	80.3

The atmospheric air contains an average of less than 1 per cent water vapor. The lung air contains about 6.2 per cent.

THE DEAD SPACE AIR

The respiratory passages extending from the nostrils to and including the terminal bronchioles (p. 295) constitute what is known as the *anatomical dead space*. The walls of these passages are relatively thick and no gaseous interchange between blood and air can occur across them. The capacity of the anatomical dead space, which was first estimated by Loewy from a cast of the respiratory passages of a dead subject, is about 150 cc. and though variable between individuals is relatively constant for the same person. During an ordinary *inspiration* about 500 cc. of air (tidal air) are inhaled. A proportion of this fresh air (150 cc.) is used to fill the dead space, the air previously in the dead space being, as mentioned above, drawn into the alveoli together with the remainder (350 cc.) of the inspired air. This 350 cc. mixes with a large volume of air (residual and supplemental airs amounting to about 2000 cc.) which remains in the lungs after the previous expiration. During *expiration* alveolar air high in carbon dioxide and low in oxygen is forced from the air sacs. Part of this is exhaled to the outside and part remains within the dead space from which it has displaced the fresh air of the previous inspiration. The expired air is therefore a mixture of alveolar and inspired airs.

The physiological dead space and its estimation

The anatomical dead space as described in the preceding section varies relatively little in capacity, though a moderate increase or decrease may occur as a result of bronchiolar dilatation or constriction. The *physiological*, *virtual* or *effective dead space* are terms applied to the total space within the lung which just prior to expiration contains perfectly fresh air, that is, air which has not diluted the alveolar air or come into contact with the respiratory epithelium. The volume of the physiological dead space varies with the depth of respiration. In shallow breathing fresh air may not be drawn as far as the terminal bronchioles. The physiological dead space would then be less than the anatomical. In ordinary breathing the physiological dead space is considerably larger than the anatomical (i.e., fresh air penetrates beyond the terminal bronchioles), and in deep breathing is enormously increased as a result of the passive dilatation of the respiratory bronchioles and alveolar ducts which after a deep inspiration receive fresh atmospheric air. The advancing margin of the latter, however, as a result of its

spike form, which has been referred to above, is prevented from coming into direct contact with the respiratory epithelium by a layer of vitiated (alveolar) air. Its gases, therefore, like those of the air of the anatomical dead space can reach the respiratory epithelium only by diffusion which, as compared with mechanical mixing, is a slow process.

The volume of the effective dead space, obviously, can only be determined by calculation. It will be equal to the volume of expired air less that of the alveolar air in the expiration. The volume of the alveolar air is derived from the volume of the expired air and the ratio of the percentages of CO_2 in alveolar and expired airs. For example, let us say that (a) the volume of air expired in a single breath is 485 cc. and (b) expired air contains 4 per cent carbon dioxide and (c) alveolar air contains 6 per cent carbon dioxide.

Then the volume of the alveolar air in the expiration is $\left(485 \times \frac{4}{6} =\right)$ 323 cc. The volume of the dead space therefore must be $(485 - 323 =)$ 162 cc. During deep breathing the ratio of the percentage of carbon dioxide in the alveolar air to that in the mixed expired air is about the same as during quiet breathing. Since the volume of the expired air is increased, the effective dead space as calculated by the above method would therefore be increased also.

Example:

Volume of expired air in a single breath	2000 cc.
Carbon dioxide in expired air	4.70 per cent
Carbon dioxide in alveolar air	6.20 per cent
Volume of alveolar air is therefore	$2000 \times \frac{4.70}{6.20} =$
1516 cc. and volume of effective dead space =	$2000 - 1516 =$
	484 cc.

CHAPTER XXXI

THE PHYSICAL PRINCIPLES GOVERNING THE RESPIRATORY EXCHANGES

The interchange of gases which occurs between the atmosphere and the air in the lungs and between the latter and the pulmonary capillaries is termed *external respiration*. Carbon dioxide diffuses from the blood to the air in the air sacs which in turn is freshened by inspired air (p. 310). Oxygen diffuses from the inspired air to the alveolar air and from this into the blood. The gaseous exchange between the systemic blood and the tissues is reversed—oxygen passing from the blood to the tissues and carbon dioxide from the tissues to the blood. This is called *internal respiration*. The gaseous exchanges are governed by physical laws—upon differences in pressures (tension) between the blood plasma on the one hand and the air or tissue fluids on the other.

Hemoglobin serves for the storage and transport of oxygen, sodium bicarbonate serves corresponding purposes for carbon dioxide (see p. 337). The actual interchange of these gases depends, however, upon their relative tensions in the different media, i.e., in the lung air, and in simple solution in the plasma and tissue fluids.

THE KINETIC THEORY OF GASES—DIFFUSION, PARTIAL PRESSURES, ABSORPTION COEFFICIENTS

Any quantity of a gas when placed in a container of whatever size expands its volume until limited by the boundaries of the confining vessel. This fact is explained upon the theory that the gas molecules are in continuous motion, moving through space at high velocity and being deflected from their course only upon coming into collision with other gas molecules or with the boundaries of the space itself from which they rebound and collide ceaselessly. Such collisions constitute a bombardment upon the confining walls which is responsible for what is called the pressure or tension of the gas. The greater the number of molecules in any given space the greater, obviously, will be the number bombarding the vessel's walls in a given time. So, if the capacity of the space is reduced the molecules are brought closer together. The rate of bombardment upon a unit of surface will increase and the pressure of the gas will rise (see *Boyle's Law* below). A rise in temperature increases the velocity of the molecular

movements, increases the rate of bombardment and the force of the impacts. The pressure in consequence increases (*Charles' Law*).

In all circumstances, the gas molecules as a result of their movements will in time distribute themselves evenly throughout the space in which they are confined and consequently the pressure will be the same upon all parts of the limiting surface. In other words, although at the start the molecules may be in greater numbers (concentration) in one part of the space than in another, even distribution is soon brought about and the pressure throughout all parts of the space becomes equal. This behavior of a gas whereby the equalization of its molecular concentration occurs is spoken of as *diffusion*. If we should deal with a mixture of two or more different gases instead of with a single gas it would be found that each component in the mixture behaved as though present alone. Its molecules would become distributed evenly throughout the mixture and its pressure would depend upon its concentration without regard to the concentrations of the other component gases (*Law of partial pressures*).

If two samples of a gas, of different concentrations be placed one on each side of a membrane permeable to that gas, diffusion also occurs until the tensions on the two sides of the membrane are equal; as in the case of a gas mixture each gas behaves as though present alone.

When a gas or a mixture of gases lies in contact with the surface of a liquid, the molecules of each gas penetrate the liquid and become dissolved in it until the tensions of that particular gas within and without the liquid are equal. The gas is then said to be equilibrated with the liquid (*Law of solubility of gases*). On the other hand, if the liquid be now exposed to a lower pressure of the gas the molecules which had undergone solution at the higher pressure escape until equilibrium is restored at the lower level. Soda water, for example, is water which has been equilibrated with carbon dioxide at a high pressure. When the cork is removed from the bottle containing the surcharged liquid, effervescence occurs. Molecules of carbon dioxide are given off until the pressure of the dissolved gas equals that of the carbon

dioxide (0.3 mm. Hg) in the atmosphere. A gas at different tensions in two liquids also comes into equilibrium whether the liquids are in direct contact or are separated by a membrane permeable to the gas. Also the actual *amount* of gas which will undergo solution at a given pressure varies with the particular gas and with the liquid. If distilled water for example be exposed to oxygen at a pressure of 760 mm. and a temperature of 0°C. each 100 cc. will take up 4.9 cc. of the gas. Oil, on the other hand, under the same conditions or pressure and temperature will absorb a great deal more. Therefore if samples of water and oil are exposed to the atmosphere though the gas pressures in the three media are identical, the volumes of the atmospheric gases in 100 cc. (volumes per cent) of each medium will be widely different.

The quantity of a gas (measured at standard temperature and pressure) which can be absorbed by 1 cc. of a liquid at 760 mm. Hg is called the

TABLE 23

Absorption coefficients of various gases in distilled water at different temperatures

TEMPER- ATURE	OXYGEN	CARBON DIOXIDE	CARBON MONOXIDE	NITROGEN
0	0.049	1.71	0.035	0.024
20	0.031	0.87	0.023	0.016
40	0.023	0.53	0.018	0.012

absorption coefficient of the gas for that particular liquid. Thus the absorption coefficient of oxygen in water at 0°C. is 0.049 and of carbon dioxide 1.71; the coefficient varies inversely with the temperature (see table 23). The presence of dissolved solid substances in the water will reduce the absorption coefficient of these gases. The values for the body fluids are therefore slightly less than those given above. Thus the coefficient of absorption of oxygen in plasma at body temperature (37°C.) is 0.024 and of carbon dioxide 0.510.

The rate of diffusion of a gas through a liquid is in direct proportion to the absorption coefficient of the gas in that liquid and inversely proportional to the square root of its molecular weight. The diffusion rate of carbon dioxide through a wet membrane is about 30 times greater than that of oxygen when the two gases are under identical conditions. For general physiological work the *diffusion coefficient* of oxygen has been defined by Krogh as the number of cubic centimeters of the gas which will diffuse 0.001 mm. distance over a square centimeter of surface, per minute, at a pressure of 1

atmosphere. It varies for different tissues and body fluids and increases 1 per cent per degree Centigrade.

The diffusion coefficients for oxygen through the following materials at body temperature were found:

Water.....	0.51
Gelatin 15 per cent.....	0.45
Muscle.....	0.31
Connective tissue.....	0.18

The diffusion coefficient of oxygen through the pulmonary epithelium of the intact animal is defined as the number of cubic centimeters which are absorbed per minute per millimeter of mean pressure difference between the blood and alveolar air. The coefficient varies in different individuals from 23 to 45 during rest and from 37 to 56 during exercise. If, for example, the mean difference between the oxygen tensions of the blood and alveolar air should be 10 mm. Hg and the coefficient 25 mm., then (10 × 25 =) 250 cc. of oxygen will be absorbed per minute. The increase in the coefficient during exercise is ascribed to the opening up of more capillaries. The differences observed between individuals are probably dependent upon the sizes of the alveoli, the thickness of the alveolar epithelium and the mean capacity of the lungs. The diffusion coefficient of carbon dioxide through the alveolar epithelium is around 500 during rest and 800 during exercise.

SUMMARY OF THE GAS LAWS

(1) *Boyle's Law.* When the volume of a gas is altered, the temperature remaining constant, the pressure varies inversely, i.e., the product of the pressure and the volume remains constant. If the space wherein a certain gas is confined be reduced by half the gas pressure is doubled and vice versa.

(2) *Law of Charles (or Gay-Lussac).* For each rise in temperature of 1°C. a gas kept at constant pressure expands by $\frac{1}{273}$ of its volume at 0°C. The volume of a gas at constant pressure is therefore proportional to its absolute temperature (–273°C.).

(3) *The Law of Partial Pressure (Dalton's Law).* The pressure exerted by a gas in a mixture of gases is equal to the pressure which the same quantity of that gas would exert were no other gases present. It follows that the total pressure of a mixture of gases is equal to the sum of the pressures of its component gases. For example, the atmosphere (dry) exerts a pressure of 760 mm. Hg. The gases of which it is composed—oxygen, nitrogen and carbon dioxide are present in the proportions of 20.96 per cent, 79 per cent and 0.04 per cent respectively. The partial pressure exerted by oxygen is therefore $\frac{20.96}{100} \times 760 = 159.2$ mm. Hg and of carbon dioxide $\frac{0.04}{100} \times 760 = 0.3$ mm. Hg.

Air in contact with water is continually receiving water molecules from the surface of the liquid. This water vapor follows Dalton's Law exerting a pressure independently of the other gases, and proportional to the quantity present in the air. The higher the temperature the greater is the quantity of water which the air will hold before becoming saturated and the greater consequently will be the tension of aqueous vapor.

The air in the lungs has a temperature of about 37°C. and is usually stated to be fully saturated with water vapor; the latter, therefore, exerts a pressure of 47 mm. Hg.¹ The air after leaving the lungs falls in temperature, some of the water vapor condenses and the latter in consequence is much less. The tension of water vapor in room air (18°C.) would be no more than 15.5 mm. Hg, even though the air were fully saturated, and is usually around 4 or 5 mm. Hg. The aqueous tensions of air (saturated) at various temperatures are given in table 24.

TABLE 24
Tension of aqueous vapor and water in grams in moisture-saturated air at different temperatures

TEMPERATURE	TENSION OF AQUEOUS VAPOR	WATER PER CUBIC METER OF AIR
°C.	mm. Hg	grams
0	4.6	4.9
5	6.5	6.8
10	9.1	9.4
15	12.7	12.8
20	17.4	17.2
30	31.6	30.1
37	47.1	

In the measurement of the respiratory gases the volumes are expressed dry (i.e., less the aqueous vapor, though actually no correction for this is required) and at standard temperature and pressure (S.T.P.)—760 mm. Hg and 0°C. The individual gases, carbon dioxide or oxygen, are then expressed as percentages of this dry volume.

In order to arrive at the tension of one or other gas from its percentage in dry air, the figure for the barometric pressure less the aqueous tension must of course be used as the basis for calculation. For example, if the carbon dioxide percentage in a sample of alveolar air (dry) is 5.6 per cent and the barometric pressure, and so of course the total gas pressure of the alveolar air,

¹ Christie and Loomis from direct measurements have obtained a lower value for the aqueous tension of alveolar air than the usually accepted one of 47 mm. Hg, (namely 45 mm. Hg). They claim that the alveolar air is not fully saturated and that the temperature of the lung is lower than has been assumed. Hyperpnea they found reduced the aqueous tension by as much as 7 mm. Hg. Holding the breath increased it by 0.5 mm. Hg.

is 760 mm. Hg, then the tension of carbon dioxide in the alveolar air must be

$$\frac{5.6}{100} \times (760 - 47) = 39.9 \text{ mm. Hg}$$

Similarly when the O₂ percentage in dry alveolar air is 14.2 the oxygen tension is

$$\frac{14.2}{100} \times (760 - 47) = 101.2 \text{ mm. Hg.}$$

(4) *Henry's Law of the Solution of Gases.* If the temperature remains constant then the quantity of a gas which goes into solution in any given liquid is proportional to the partial pressure of the gas.

THE EXCHANGE OF GASES IN THE LUNGS
THE PARTIAL PRESSURES OF THE GASES IN THE LUNG AIR

In table 25 are given average figures for the partial pressures of oxygen, carbon dioxide and nitrogen in inspired, expired and alveolar airs.

TABLE 25			
BAROMETER 760 MM. Hg	PARTIAL PRESSURE		
GAS	Inspired air	Expired air	Alveolar air
	mm. Hg	mm. Hg	mm. Hg
Oxygen.....	158.25	116.2	101.2
Carbon dioxide.....	0.30	28.5	40.0
Nitrogen.....	596.45	568.3	571.8
Aqueous vapor.....	5.00	47.0	47.0
Totals.....	760.00	760.0	760.0

The fall in oxygen pressure from inspired to alveolar air and in the reverse direction for carbon dioxide will quite evidently promote the free interchange of these gases within the lung. The interchange of gases between inspired and alveolar airs is reflected in the intermediate values shown for the gas pressures in the expired air.

The alveolar oxygen and carbon dioxide tensions vary with the minute volume (p. 350). During hyperpnea the CO₂ tension falls and the O₂ tension rises. When the breath is held or during periods of apnea changes of a reverse order occur.

Nitrogen, so far as respiration is concerned is inert. A small but constant amount (about 0.83 volume per cent) of the gas is taken up and dissolved in the plasma but it is neither used nor

produced within the body, the quantities in arterial and in venous blood being identical. It will be noted, however, that the percentage of this gas is higher in expired than in inspired air (see p. 311). This is due not to any absolute increase in the quantity of nitrogen but is related to the reduction of the total volume of the respiratory gases resulting from the greater quantity of oxygen absorbed than carbon dioxide put out.

THE PARTIAL PRESSURES OF OXYGEN AND CARBON DIOXIDE IN BLOOD

In table 26 are given the tensions of oxygen and carbon dioxide in arterial and in venous blood. The venous blood, it will be seen, has a lower tension of oxygen (by 60 mm.) than the alveolar air but a higher tension of carbon dioxide (by 6 mm.). It is to be remembered that the pulmonary capillaries and the air in the alveoli are

TABLE 26
Gas tensions in arterial and in venous blood

	TENSION	
	Venous blood	Arterial blood
	mm. Hg	mm. Hg
Oxygen.....	40	100
Carbon dioxide.....	46	40
Nitrogen.....	570	570
Water vapor.....	47	47
Totals.....	703	757

separated by delicate membranes freely permeable to these gases. The pressure gradients are favorable to a rapid inward diffusion of oxygen (from alveolar air to blood) and an outward diffusion of carbon dioxide (from blood to alveolar air). Equilibrium is quickly established between the respiratory gases in the alveolar air and in the blood of the pulmonary capillaries. Since the diffusion coefficient of carbon dioxide through the pulmonary membrane is much higher than that of oxygen, the pressure gradient need not be so high for the former gas. It will be seen from tables 25 and 26 that the tension of carbon dioxide in the blood leaving the lungs, i.e., in the mixed arterial blood, is the same as that in the alveolar air. Indeed, it is the usual practice, when one wishes to know the arterial CO₂ tension, to determine that of the alveolar air and assume that the two are identical. It has been shown, however, by Bock and associates that a slight difference

(0.5 mm. Hg) does exist. The tension of oxygen in arterial blood is from 5 to 10 mm. Hg below that of the alveolar air, i.e., from 95 to 100 mm. Hg.² (See fig. 144 and footnote on p. 317.)

Gaseous equilibrium is attained not instantaneously but progressively along the course of the pulmonary capillary. Diffusion is rapid at the venous end but as blood and alveolar air approach equilibrium the diffusion process necessarily becomes slower. The length of the capillary and the rate of the blood flow through it are factors which must determine the extent to which equilibrium occurs. As a matter of fact though the circulation through the lungs be speeded up several fold the oxygenation of the blood or the elimination of carbon dioxide is little impaired. It is also true that though the blood coming to the lungs has given up 50 per cent or more of its oxygen-

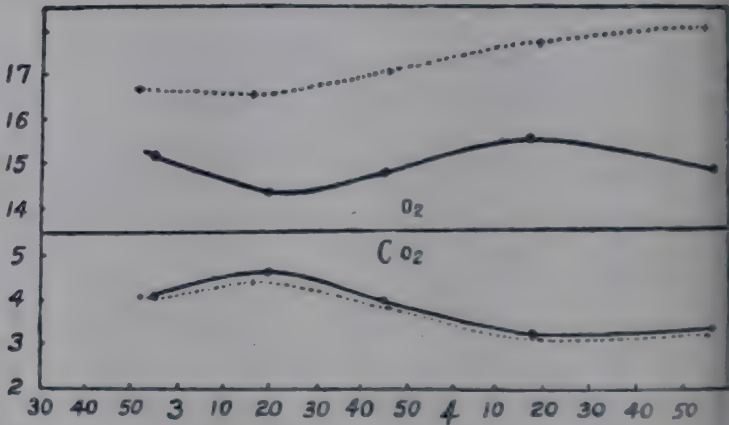


FIG. 144. Curves showing relationship between O₂ and CO₂ tensions in alveolar air (dotted lines) and arterial blood (continuous lines) of rabbit. Gas tensions, in per cent of an atmosphere, along ordinate; time along abscissa. (From A. and M. Krogh.)

load to the tissues, the uptake of oxygen and the elimination of carbon dioxide are effected without difficulty by healthy lungs, for the diffusion rates are greatly increased as a result of the larger differences which must then exist between the gas tensions in alveolar air and venous blood.

The tensions of oxygen and carbon dioxide in human arterial blood may be determined by bringing a small bubble of air into contact with a sample of the blood obtained by arterial puncture. The method employed for the purpose is an adaptation to man (Barcroft and Nagahashi) of a method originally invented by Krogh for animals (see fig. 145). After the gases in the air have come into equilibrium with those dissolved in the blood the small bubble is analyzed and its composition determined. The gas tensions are

² Bock and his associates find a much greater difference than this between the oxygen tension of the alveolar air and arterial blood

then calculated from their percentages (p. 315). Since no gaseous exchanges occur across the walls of the arteries, the tensions so determined are those of the mixed arterial blood of the pulmonary capillaries. It has already been mentioned that the arterial carbon dioxide tension is usually obtained from an analysis of alveolar air. The gas tensions of the blood coming to the lungs—the *mixed venous blood*—is usually determined in man by indirect methods (p. 228). In animals mixed venous blood may be obtained from the right ventricle by puncturing the chest wall with a hollow needle attached to a syringe.

THE VOLUMES OF OXYGEN AND CARBON DIOXIDE IN BLOOD

Knowing the respective absorption coefficients for oxygen and carbon dioxide in plasma, and the gas pressures, the volume of each gas in simple solution in 100 cc. of plasma can be readily calculated (table 27). For example, the absorption coefficient of oxygen in plasma is 0.023 at body temperature and at a pressure of 760 mm. Hg. At the partial pressure of oxygen in arterial blood the plasma should hold in solution $\frac{100}{760} \times 0.023 = 0.003$ cc. of oxygen per cubic centimeter or 0.3 volume per cent. In *whole blood* the quantity of oxygen in *simple solutions* is less—only 0.24 volume per cent. The absorption coefficient of carbon dioxide in plasma (0.51) or of whole blood is higher (0.48) than that of oxygen but the partial pressure of carbon dioxide to which arterial blood is exposed in the lung is lower (40 mm. Hg) than that of oxygen. The quantity of the former gas in simple solution in whole blood is therefore $\frac{40}{760} \times 0.48 = 2.5$ volumes per cent.

Nineteen volumes per cent of oxygen and from 40 to 55 volumes per cent of carbon dioxide can be removed from arterial blood. The proportions of these gases present in simple solution must, therefore, be only a small fraction of the quantities held in the blood in other ways. They are present in chemical combination—oxygen with hemoglobin and carbon dioxide mainly as bicarbonate (see Chap. XXXIII).

Blood normally contains about 15 grams of hemoglobin per 100 cc. Since 1 gram of hemoglobin carries a maximum of 1.34 cc. of oxygen, arterial blood would, therefore, when saturated to its full capacity, contain about 20 cc. of oxygen. Blood as it leaves the lungs is from 94 to 96 per cent saturated with oxygen so that the hemo-

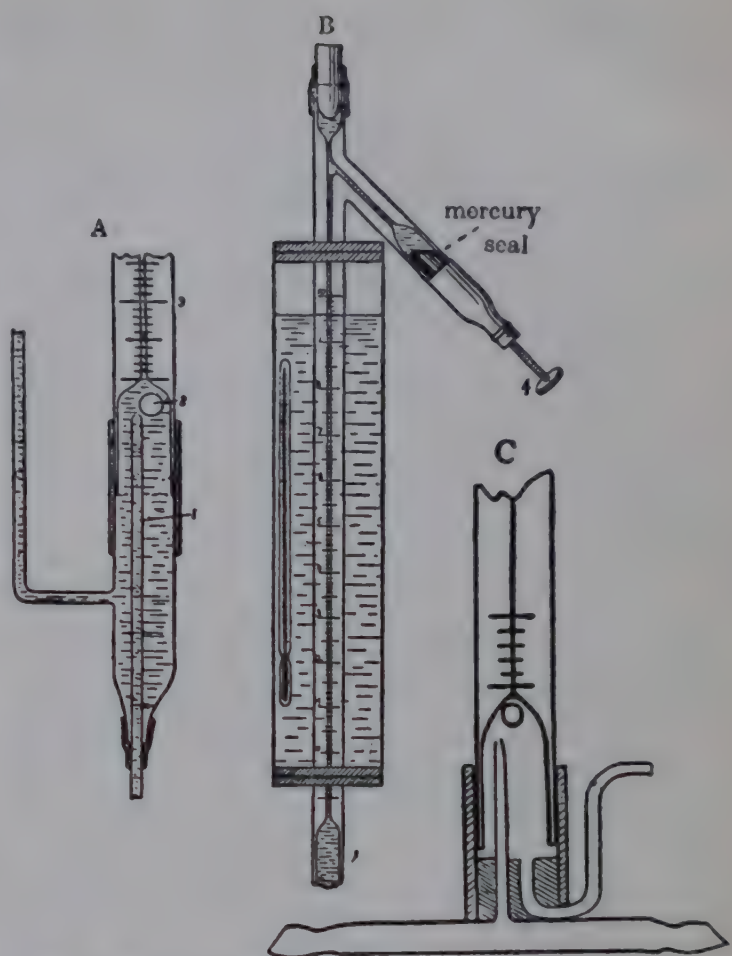


FIG. 145. Krogh's microtonometer. A is an enlarged view of an equilibration chamber constituting the lower part of B(1) but which is shown only in part in the latter drawing. A is filled with saline solution through the side tube. 1, a narrow tube into which the specimen of blood is introduced; 2, an air bubble. The lower end of 1 is connected by rubber tubing to a cannula inserted into a blood vessel; the blood issues from a narrow opening at the upper end of the tube 1 in a fine jet and plays upon the bubble. After the gases in blood and bubble have come into equilibrium the latter is drawn into the graduated capillary tube shown in B, by means of the screw-plunger (4), and analyzed according to the following procedure. The volume of the bubble is first measured, it is next drawn into a solution of KOH which absorbs the CO_2 , then returned to the graduated tube and measured again; the difference between the two measurements gives the amount of CO_2 which it contained. The bubble is then passed through a solution of potassium pyrogallate, to absorb the O_2 , and its volume measured a third time. C is a model with an attached cannula which can be inserted directly into a blood vessel.

globin holds at this degree of saturation only about 19 cc. of oxygen per 100 cc. of blood.*

* Since the blood in passing through the capillaries of an air sac comes into equilibrium with the air of that air sac as described on page 310 the statement that the arterial blood has a tension less than that of the alveolar air and is only from 94 to 96 per cent saturated, requires explanation. The discrepancy is explained as follows. The air sacs are not all ventilated to the same extent; in some the O_2 tension is higher, in some lower than that of the alveolar air as determined upon a sample. In other words the O_2 tension of a sample of alveolar air is an average of the O_2 tensions of the air in all the air sacs. But, when we come to consider the blood coming, not from a single air sac, but from the lung as a whole—i.e., the *mixed arterial blood*—

The quantity of oxygen or of carbon dioxide contained in a given sample of blood (*oxygen or*

TABLE 27

Volumes per cent (cubic centimeters of gas per 100 cc. blood) of oxygen and carbon dioxide in arterial and in venous blood

GAS	VENOUS BLOOD		ARTERIAL BLOOD	
	Total	In simple solution	Total	In simple solution
Oxygen	12-14	0.1	19.0*	0.24
Carbon dioxide	58	3.0	52	2.5

* As determined by the method of Van Slyke.

carbon dioxide content) is determined by transferring the sample to a blood-gas apparatus (Haldane

it becomes evident that while an under-ventilated air sac will lower the oxygen tension and so the oxygen saturation of the hemoglobin, an over-ventilated one cannot compensate this effect to any significant extent. The O₂ in solution (upon which the O₂ tension directly depends) is in equilibrium with that combined in hemoglobin and it is evident from the shape of the O₂ dissociation curve of hemoglobin that a rise in oxygen tension above 100 mm. Hg will saturate the blood very little more whereas a fall of 20 mm. Hg or so will reduce the saturation very materially (see also shallow breathing p. 365).
The variation between individuals in the O₂ saturation of the arterial blood is attributed to the different degrees to which uneven ventilation of the air sacs occurs and also to slight differences in the shapes of the dissociation curves. It was first shown by Barcroft that the O₂ dissociation curve is not precisely the same for all persons. The dissimilarities are due apparently to slight differences in the chemical constitution of the globin part of the hemoglobin molecule.

or Van Slyke) and then freeing all the oxygen from the hemoglobin by the addition of potassium ferricyanide, or all carbon dioxide from combination by the addition of acid. Precaution must be taken not to permit the sample to come in contact with air. Since the cell wall is not freely permeable to K₃Fe(CN)₆ the corpuscles should be first laked by ammonia or saponin solution. Haldane showed that all the oxygen in blood is liberated by this procedure and the oxyhemoglobin is turned into methemoglobin (p. 00). The method most commonly used is that of Van Slyke (described in Peters and Van Slyke, Quantitative Clinical Chemistry (Methods)). The *oxygen capacity* of a sample of blood is calculated by exposing it to air or oxygen and determining the amount which it then contains, that is, when the hemoglobin is completely saturated. The ratio of oxygen content to oxygen capacity × 100 gives the percentage saturation of the blood with oxygen. Since the quantity of oxygen (1.34 cc.) which will combine with 1 gram of hemoglobin is known, the hemoglobin content of a specimen of blood may be calculated from the quantity of O₂ in the blood when fully saturated, i.e., from its oxygen capacity. For example, if a sample of blood has an oxygen capacity of 10 volumes per cent its hemoglobin content is $\left(\frac{10}{1.34} = \right)$ 7.5 grams per cent or 50 per cent of the normal.

CHAPTER XXXII

THE TRANSPORT AND DELIVERY OF OXYGEN TO THE TISSUES

Hemoglobin serves for the storage and transport of oxygen. The small amount of oxygen in simple solution (about 1 per cent of the total) is negligible when one considers the oxygen requirements of the tissues (250 cc. per minute) even under ordinary conditions. If the blood could hold no more than this it would be necessary for some 120 liters to circulate through the tissues each minute, even assuming that all the oxygen were given up during each circulation. Nevertheless, the gas in simple solution is of the utmost importance since it is in equilibrium with the alveolar air on the one hand and on the other determines the quantity of oxygen which shall be held in combination with the hemoglobin. This will be made clear from a study of the oxygen dissociation curve for hemoglobin.

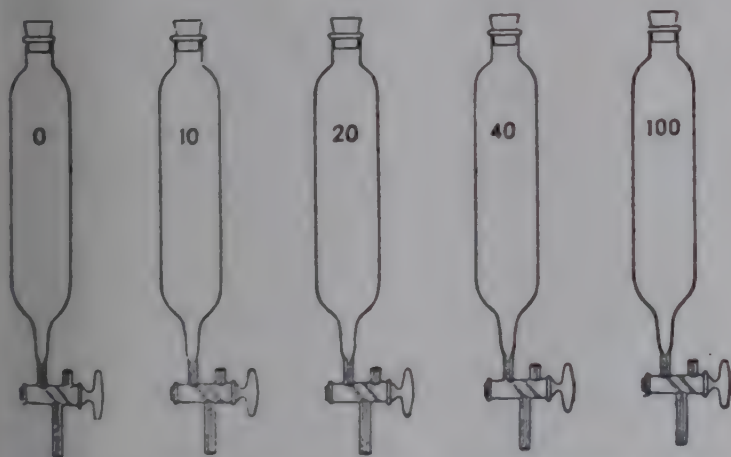


FIG. 146. Series of tonometers. The numbers denote the pressure of oxygen in mm. (After Barcroft.)

THE DISSOCIATION CURVE OF HEMOGLOBIN

Oxygen enters into chemical combination with the iron of the hemoglobin molecule (see p. 43) to form oxyhemoglobin. Each atom of the metal unites with two atoms of oxygen. The remarkable feature of the union of oxygen with hemoglobin is the readiness with which the gas is released from combination when its tension in the surrounding medium is reduced. Hemoglobin from which the oxygen has dissociated is called reduced hemoglobin. The relationship between the partial pressure of oxygen and the percentage saturation of the hemoglobin with the gas—i.e., the proportion of oxyhemoglobin to reduced hemoglobin—can be shown in the form of a curve—the *oxygen dissociation curve of hemoglobin*. The curve for a

solution of hemoglobin in distilled water is obtained in the following manner. Several samples of the hemoglobin solution are placed each in a separate closed vessel known as a tonometer (fig. 146). The respective samples are then exposed to known oxygen tensions: 0, 10, 20, 40 and 100 mm. Hg. The tonometers are rotated continuously in a water bath at body temperature. The solution is thus spread out as a thin film over the interior surface of the vessel. After equilibrium has been attained the proportion of oxy- to reduced hemoglobin is determined. When 100 per cent saturated the solution contains about 20 volumes per cent of oxygen. When a quarter or half saturated

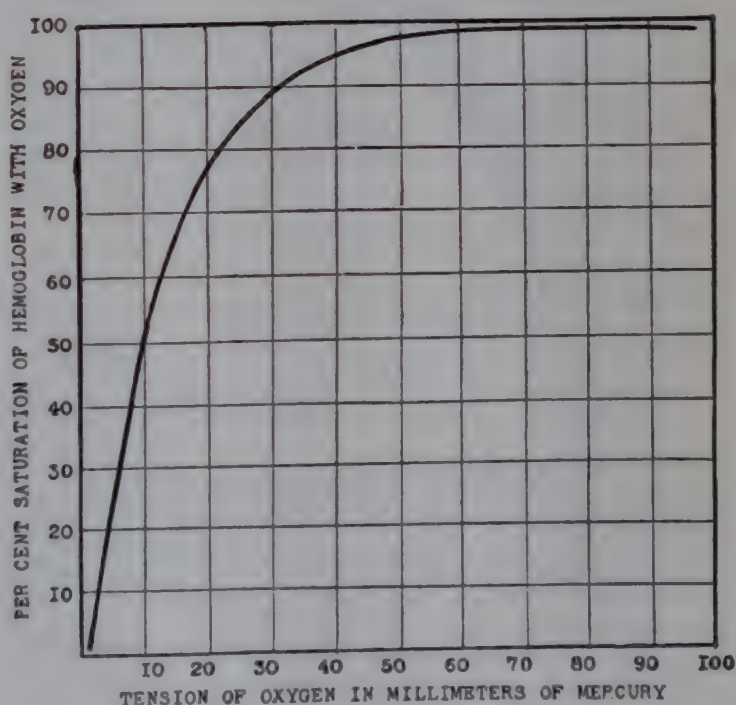


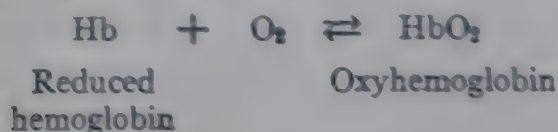
FIG. 147. Oxygen dissociation curve of a solution of hemoglobin. (After Barcroft.)

it therefore contains 5 to 10 volumes respectively. The results are plotted on a chart with the oxygen tensions along the abscissae and the percentage saturation along the ordinates as shown in figure 147. The curve is a rectangular hyperbola. Huffer obtained such a curve for hemoglobin from calculations based upon the law of mass action (see below).

If the foregoing procedures are carried out with blood instead of with a hemoglobin solution a different type of curve is obtained as shown in figure 148. It is doubly inflected or S-shaped.

The dependence of the oxygen saturation of

hemoglobin in an aqueous solution upon the partial pressure of the gas is in accordance with the law of mass action which states that "the velocity of chemical change is proportional to the product of the concentrations of the reacting substances." In this case the reacting substances are reduced hemoglobin and oxygen. The reaction is reversible and is represented thus



It is evident that in the foregoing procedures the tension of oxygen in the hemoglobin solution, or in the plasma in the case of whole blood, came into

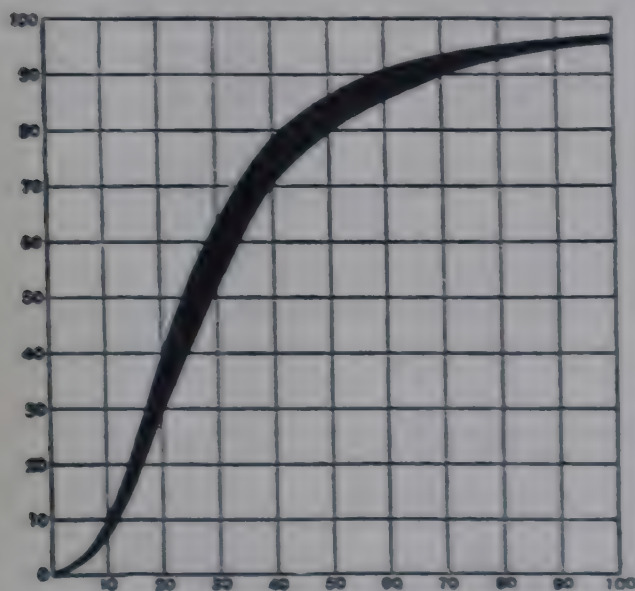
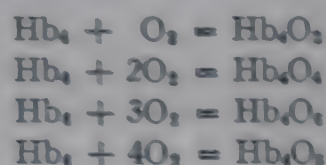


FIG. 148. Composite curve to show the degree of variation in the oxygen dissociation curve of human blood as determined upon a number of persons. In each case the blood was exposed to an atmosphere containing the same percentage of CO_2 as that of the alveolar air of the individual examined. Ordinates, percentage saturation; abscissae, oxygen pressure. (After Barcroft.)

equilibrium with the oxygen pressure of the atmosphere introduced into the tonometer. Then, the concentration of the dissolved oxygen must be proportional to the partial pressure of the gas to which the solution was exposed (p. 313). So, if C_o = concentration of O_2 , C_r = concentration of reduced hemoglobin and C_a = concentration of oxyhemoglobin, then the velocity of the reaction of Hb with O_2 to form HbO_2 will be proportional to the product of C_o and C_r multiplied by a constant k , and the reverse reaction, the dissociation of oxyhemoglobin (HbO_2) to reduced hemoglobin (Hb) and oxygen, will be proportional to C_a multiplied by another constant k_1 . Thus:

$$k(C_o \times C_r) = k_1(C_a)$$

At any given tension of oxygen in the opposite reactions, the formation of oxyhemoglobin and its dissociation proceed simultaneously until equilibrium becomes established. A simple reaction of this nature will explain the dissociation curve of a hemoglobin solution but the S-shaped curve of blood is thought to be due to a series of reactions. It will be recalled that natural hemoglobin (p. 43) has a molecular weight (68,000), four times greater than was previously supposed. It may therefore be given the symbol Hb_4 . It is thought that each molecule of hemoglobin combines with four molecules of oxygen, $\text{Hb}_4 + 4\text{O}_2 \rightarrow \text{Hb}_4\text{O}_8$. The oxygen dissociation curve calculated by the application of the law of mass action to this equation has more pronounced S-shape than any actually observed for blood. On the other hand, the curve calculated from the equation $\text{Hb}_4 + \text{O}_2$ is hyperbolic (fig. 147). It is believed, therefore, that the combination of oxygen with hemoglobin under physiological conditions, four separate but simultaneous reactions take place.



The combination of all these reactions, it has been suggested, is responsible for the special S-shape of the oxygen dissociation curve (figs. 148 and 149).

Certain features of the oxygen dissociation curve of whole blood shown in figure 149 are of the most physiological importance. It will be seen that at 100 mm. Hg, i.e., at the partial pressure of oxygen in arterial blood, hemoglobin is about 95 per cent saturated. Increasing the oxygen tension beyond 100 mm. Hg will therefore increase very little the quantity of oxygen with which the hemoglobin can combine. The flattening out of the upper part of the curve means that relatively little reduction in the percentage saturation of the hemoglobin occurs until the oxygen pressure falls to about half its normal value. At an oxygen tension of 70 mm. Hg the hemoglobin is about 90 per cent saturated. The slope of the lower part of the curve is such that a given fall in oxygen pressure causes a much greater desaturation of the hemoglobin. The behavior of hemoglobin as indicated by the shape of its curve therefore favors a nearly maximum uptake of oxygen in the lungs so long as the oxygen pressure is above 70 mm. Hg and a rapid liberation of the gas at lower oxygen pressures which prevail in the tissues. It will be realized from a glance at the hyper-

ve shown in figure 147 how unsuitable hemoglobin would be as a carrier of oxygen if it behaved in the manner indicated by this curve. The hemoglobin would show a great avidity for oxygen in the lungs but would not yield up its oxygen until the partial pressure in the tissues had fallen to a very low level. At the pressures which exist in the tissues the rate of dissociation of hemoglobin would be many times slower than the rate of its formation. Hemoglobin would thus be worthless as an oxygen carrier. As it is, the oxygenation of hemoglobin in the lungs and the reduction in the tissues proceed at practically equal rates.

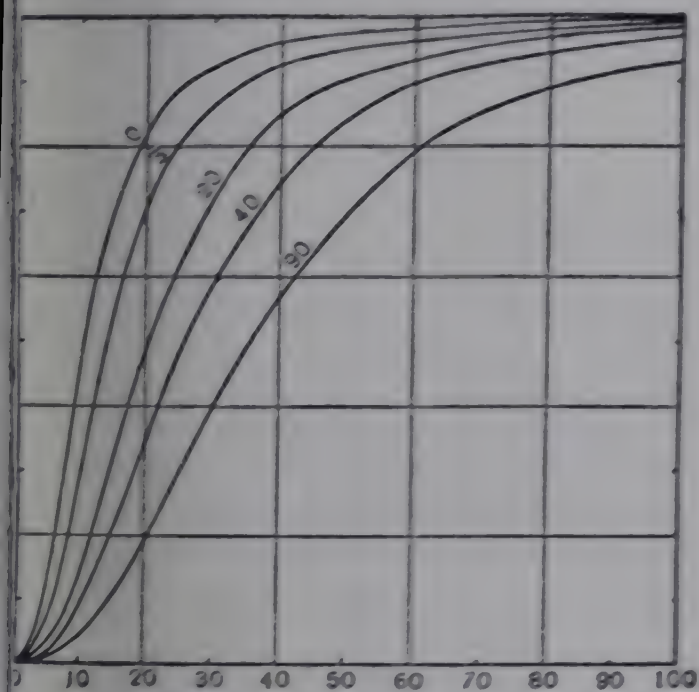


FIG. 149. Dissociation curves of human blood, exposed to 0, 3, 20, 40 and 90 mm. CO_2 . Ordinates, percentage saturation. Abscissae, oxygen pressure. (after Barcroft.)

THE EFFECTS OF REACTION AND OF TEMPERATURE UPON THE SHAPE OF THE OXYGEN DISSOCIATION CURVE

The effect of dissolved inorganic salts upon the shape of the dissociation curve appears to be of less importance than was previously supposed. Hemoglobin solutions free from salts give the S-shaped curve when special precautions are taken to prevent a change (denaturation) occurring in the natural constitution of the hemoglobin complex. Denaturation may result from bacterial action, "ageing" or other agencies.

The oxygen dissociation curve of hemoglobin is so sensitive to acid that it has been used by Barcroft and associates as a basis of a method for measuring changes in blood reaction. A shift of the curve to the right, i.e., when the blood absorbs less oxygen at a given pressure, would indicate an increase in H^+ ion concentration, and a shift to the left the reverse change.

A change in the reaction of the blood toward the acid side causes the curve to flatten toward the right, i.e., the affinity of hemoglobin for oxygen is reduced. Carbon dioxide and lactic acid liberated during tissue activity will exert this effect. The influence exerted by CO_2 was discovered by Bohr and is usually referred to as the Bohr effect¹ (see figure 149). Temperature exerts a similar effect upon the dissociation curve. These agencies, therefore, cause the hemoglobin to liberate its oxygen more readily at the lower oxygen tensions but exert little effect upon the uptake of oxygen at the higher tensions; they cause the reactions involved in the breakdown of oxyhemoglobin to be speeded up, the equilibria shown on page 320 being shifted to the left. Alkalis and a fall in temperature will of course have the reverse effect.

THE UNLOADING OF OXYGEN IN THE TISSUES

It is now possible to give a connected account of the manner in which oxygen is taken up from the lungs by the blood and supplied to the tissues. The absorption of oxygen from the alveolar air is the result simply of diffusion (pp. 313 and 314). The oxygen tension in the arterial blood is lower (never higher) than that of the alveolar air. This is so, even at high altitudes where the alveolar oxygen tension is greatly reduced (p. 361). There is no reason, therefore, to believe that the pulmonary epithelium actually secretes oxygen into the blood.² The percentage saturation of the hemoglobin is dependent upon the oxygen tension of the blood, i.e., the amount of the gas in simple solution, which, as just mentioned, is governed in turn by the oxygen pressure in the alveolar air. The hemoglobin in the blood leaving the lungs is about 95 per cent in the form of oxyhemoglobin (i.e., it is 95 per cent saturated).

Practically no oxygen is lost from the arterial blood until the capillaries have been reached, so the blood reaches the periphery with a high pressure head of oxygen. The oxygen tension of the tissue fluids and cells is relatively low; a flow of oxygen from the plasma across the capillary membrane results. This, of course, will tend to lower the oxygen tension of the capillary blood plasma and upset the equilibrium between it and the oxyhemoglobin. Dissociation of the latter occurs to sustain the partial pressure of the plasma oxy-

¹ The view that the pulmonary epithelium does not always play the rôle of a passive membrane but is capable of actively secreting oxygen into the arterial blood was advanced by Bohr and has been elaborated by Haldane.

gen. In other words a steady flow of oxygen from red cell to tissue cell is maintained as a result of the slope in partial pressure of the gas. The rise in temperature and liberation of carbon dioxide and lactic acid in the tissues, as we have seen, shifts the oxygen dissociation curve to the right and so accelerates the decomposition of the oxyhemoglobin.

COEFFICIENT OF OXYGEN UTILIZATION

In passing through the capillaries the blood under ordinary circumstances loses from a fifth to a quarter of its oxygen store. That is, the hemoglobin in the blood coming to the lungs has an oxygen saturation of from 70 to 75 per cent, the tension of the gas being between 35 and 40 mm. Hg. The figure used to express the proportion of the total oxygen content of the blood which is given up to the tissue is called the *coefficient of oxygen utilization*. Thus, if the oxygen content of the arterial blood is 19 volumes per cent and that of the venous blood 12 volumes per cent (i.e., arterio-venous oxygen difference 7 per cent) the coefficient is ($\frac{7}{19} =$) 0.36. The coefficient varies considerably for different tissues and for the same tissue in accordance with the degree of its activity and rate of blood flow. During very strenuous exercise for example the hemoglobin of the venous blood coming from the muscles may be only 25 per cent saturated with oxygen. Heart muscle has a very high coefficient.

THE RESPIRATORY QUOTIENT

The ratio of the volume of carbon dioxide produced by a tissue to the volume of oxygen absorbed

$$\frac{\text{Volumes CO}_2 \text{ produced}}{\text{Volumes O}_2 \text{ absorbed}}$$

is called the respiratory quotient of that particular tissue. The ratio of these volumes as determined from the expired air will be the respiratory quotient of the body as a whole (p. 523).

THE MANNER IN WHICH THE CALL OF THE TISSUES FOR OXYGEN IS MET

Increased activity of any tissue always entails an increased oxygen consumption which may be several times the resting value. Increase in the oxygen supply to the tissue above its requirement on the other hand does not increase the oxygen usage. The tissue takes what oxygen its activity at the moment demands but no more.

There are two ways in which a greater demand of the tissues for oxygen may be met. By (1) increasing the total blood flow through the tissue and maintaining a high intracapillary oxygen pressure, and (2) raising the coefficient of oxygen utilization, i.e., increasing the quantity of oxygen abstracted from a given volume of blood.

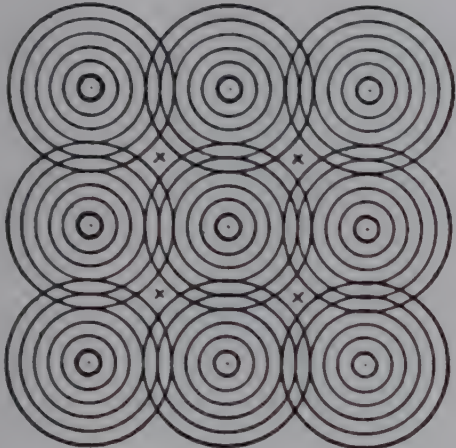
Both these factors come into play but the extent to which each operates is not the same for different tissues. The coefficient of oxygen utilization is increased by establishing a steep oxygen pressure gradient between the plasma within the capillaries and the tissue cells. That is, the quantity of oxygen used (Q) will, other things being equal, be proportional to the difference in intracapillary and intracellular pressures (P_c and P_t respectively), thus:

$$Q \propto P_c - P_t$$

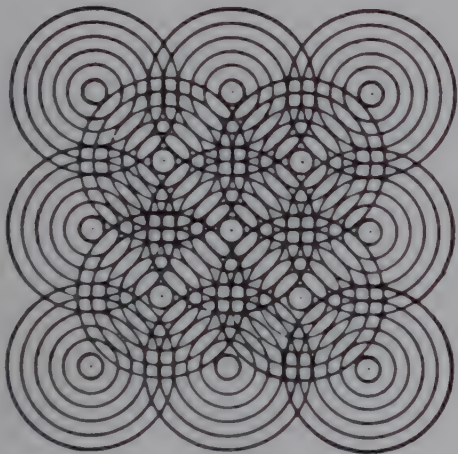
An increase in the pressure gradient is brought about, (a) by the action of acids (carbonic and lactic) and a rise in temperature both of which accelerate the decomposition of oxyhemoglobin and so maintain a high intracapillary oxygen pressure, (b) by lowering the oxygen tension within the tissue cells, and (c) by shortening the distance through which the oxygen must diffuse, i.e., by opening up more capillaries and so reducing the radius of the cylinder of tissue supplied by each capillary (fig. 150). The oxygen tension of resting skeletal muscle is low—about 20 mm. Hg or less. During activity therefore little increase in the pressure gradient can result from a reduction in the intracellular oxygen tension even if this falls to zero. In muscular activity, the greatly increased oxygen supply is the result mainly of augmented blood flow and the increase in the coefficient of oxygen utilization produced by (a) and (c) above.

During strenuous exercise the coefficient of oxygen utilization of the muscles may be more than doubled and the blood flow through the muscles increased several fold. If, for example, a two-fold increase in the coefficient of oxygen utilization occurred together with a four-fold increase in blood flow the actual amount of oxygen delivered to the contracting muscles would be increased ($2 \times 4 =$) 8 times. In man the oxygen consumption of the muscles may actually be increased by from twenty to thirty times or in an athlete even fifty times. It has been found that the resting gastrocnemius of the cat consumes on the average 0.003 cc. of oxygen per gram of muscle

per minute. During activity the blood flow increases some 6 times, and the oxygen consumption over seven-fold. The increase in oxygen consumption must be brought about in part by the removal of more oxygen from each unit of blood. A marked rise in the coefficient of oxygen utilization has been demonstrated by several observers in man during exercise.



A



B

FIG. 150. The pressure of oxygen in the tissues. The dot in the center of each series of concentric circles represents a capillary containing blood with an oxygen pressure of 30 mm. Hg. Between each circle and the next larger one there is a fall of 5 mm. Hg. in oxygen pressure. At the points marked X (in A) the oxygen pressure is therefore zero, and the tissue is asphyxiated. In B, extra capillaries have opened up and there is a finite oxygen pressure throughout the tissue. (After Barcroft.)

The circulation rate (p. 224) in man may increase nearly ten-fold during muscular exercise. It is certain, however, that there is also a redistribution of the blood, that is, a greater *proportion* of the total blood volume is driven through the muscles than during rest. The actual blood flow through the active muscles may, for this reason, be twenty times or more greater than the flow during rest, though the blood flow through the body as a whole is increased only ten times or so. In exercise, then, though the red cell has a shorter

stay in the capillary it unloads more of its oxygen, as indicated by the increase in the coefficient of oxygen utilization. The actual speed of the red cell through the capillary is not, however, as great as might be thought from the increased volume of blood flowing through the muscles, for the opening up of more capillary channels and the consequent increase in the total cross section of the blood stream (p. 148) tends to prevent any excessive acceleration of the red cell's passage.

INTRACELLULAR OXIDATION AND THE BIOLOGICAL TRANSFORMATION OF ENERGY

By A. M. WYNNE

No problem in the entire field of physiological and biochemical investigation is of greater fundamental significance than is that which concerns the transformation of energy in living organisms; for it is through the transformation of energy that life itself is made possible. What are the special characteristics which distinguish living matter from all other structures? This question cannot be answered in precise terms: the word 'living' is used to embrace such a wide variety of structures that no universally acceptable characterization of living matter is possible. Indeed, the transition from the 'living' to the 'non-living' state is so gradual that it is quite impossible to draw a sharp line of division between the two states. But, if one may exclude the border-line systems and confine the discussion to the great variety of structures concerning whose living nature there can be no disagreement, it is possible to identify certain properties which distinguish the living cell from other structures. For example, the structure of the cell, with its multiplicity of surfaces, makes possible the orderly interplay and progression of a great variety of chemical reactions which take place within the boundaries of the cell and are co-ordinated with reactions in neighboring cells and fluids. Moreover, the living cell is able to liberate from cellular metabolites their stores of potential chemical energy in the form of free energy and to utilize free energy in the performance of work of many kinds, including the synthesis of specific cellular substances of varying complexity from non-specific materials. All this is accomplished at ordinary temperatures and in media which are nearly neutral. It is true, of course, that only a relatively small and somewhat variable fraction, usually not more than 20 or 25 per cent, of the total free energy released in catabolic reactions can be utilized in the anabolic and dynamic activities of the organism. The remainder is transformed into heat; and, since the living organism cannot utilize heat energy in the performance of work, a large proportion of the energy released in cellular metabolism serves no useful purpose except that of maintaining the temperature of the organism, and is soon lost to the environment.

"The living cell is not only the smallest independent unit of biological structure but it is also the smallest unit capable of maintaining complete metabolic activity". The metabolic activity of the cell is an expression of the dynamic inter-relationships of chemical reactions, many of which are concerned with the liberation, interchange or utilization of free energy; the great majority of the reactions are, moreover, controlled and co-ordinated by specific colloidal catalysts, called enzymes, functioning in heterogeneous media in which surfaces and spatial orientation play a predominant role.

It is the main purpose of this section to discuss briefly some of the enzymes which are concerned with the oxidation and reduction of cellular substances, and, in particular, to inquire into their mode of action in relation to the oxidation-reduction systems of the cell which are responsible for the transport of hydrogen and electrons from the metabolites to molecular oxygen. These enzymes are essential components of the catalytic systems which exercise control over the intracellular oxidative reactions which provide the organism with a large proportion of its supply of free energy. Later in the chapter, reference will be made to recent investigations of coupled reactions in which energy released in oxidative processes is trapped in the form of energy-rich phosphate bonds and is subsequently made available to the cell for the performance of work.

Oxidations in general can be accomplished by the addition of oxygen, by the removal of hydrogen or by the withdrawal of electrons. All three methods are fundamentally similar in principle; for, in each case, there is a loss of one or more electrons from the substance undergoing oxidation. Reduction, on the other hand, means, primarily, a gain of electrons, though the actual mechanism of reduction may involve the addition of hydrogen or the loss of oxygen. In biological systems the direct union of molecular oxygen with cellular metabolites has never been satisfactorily demonstrated although oxygen is, of course, the ultimate oxidizing agent in all aerobic organisms. While it is true that oxygen may be added to the molecule, as in the oxidation of an aldehyde to an acid, it is not molecular oxygen which is added, but, rather, oxygen which has its origin in some other source such as water or phosphate. In the case of the majority of the metabolites concerning whose physiological oxidation anything definite is known, the primary oxidation is effected by the removal of two hydrogen atoms (or two hydrogen ions and two electrons) through the agency of a specific dehydrogenase. It is with this hydrogen that oxygen eventually reacts, to form either water or hydrogen peroxide. The union of the liberated hydrogen with oxygen may be a direct one in the case of a relatively few dehydrogenases, such as certain flavoproteins whose activity leads to the formation of H_2O_2 . In other cases, the liberated hydrogen atoms, or hydrogen ions and electrons derived from them, are believed to be transported to molecular oxygen by a series of reversible oxidation-reduction systems. The

hydrogen is oxidized to water, and free energy is liberated. The molecular oxygen which takes part in oxidative reactions finally appears, therefore, only in the form of water, as the result of oxidation of hydrogen. No molecular oxygen enters directly into the formation of CO_2 ; the oxygen contained in this product of respiration was either present originally in the compound oxidized or was added to it, in the form of water or of phosphate, at some intermediary stage of oxidation.

Oxidation-reduction potential. An oxidation-reduction (O-R) system contains two chemically related components which are capable of reversible transformation by the transfer of one or more electrons (or of H-ions and electrons). The relationship between the reduced and oxidized components (frequently called the 'reductant' and 'oxidant' respectively) may be represented by the equation

reduced component \rightleftharpoons oxidized component + $n e$
where n represents the number of electrons (e) transferred. The oxidizing or reducing power of such a reversible system in relation to that of other similar systems depends on two main factors: (1) a capacity factor which is governed by the concentration or, more accurately, the 'activity' of the reactants, and (2) an intensity factor which is a fundamental property dependent upon the nature of the substances concerned. The intensity factor is the characteristic oxidation-reduction potential of the system and is represented by the symbol E_o in the equation

$$E_h = E_o + \frac{RT}{nF} \ln \frac{[\text{Oxidant}]}{[\text{Reductant}]}$$

where E_h is the potential (in volts) of an inert metallic electrode measured in a system of arbitrarily chosen ratio of [Oxidant] to [Reductant], and referred to the normal hydrogen electrode, at absolute temperature T . R is the gas constant, expressed in electrical units, n is the number of electrons transferred, and F is the faraday. E_o is the normal potential of the system at $pH = 0$, referred to the normal hydrogen electrode when $[Ox] = [Red]$. When the concentrations of oxidant and reductant are equal the ratio is unity and the logarithm zero; then $E_h = E_o$. The normal hydrogen electrode ($pH = 0$) has been arbitrarily assigned a potential of zero. On increasing the pH at constant temperature, the potential of the H electrode decreases by approximately 0.06 volt for each unit of pH ; at $pH 7.0$ its potential is -0.421 . Similarly, the potential of other systems may be affected by changes in pH if, for example, the ionization of the reactants is influenced by pH -changes. And since the determination of the O-R potentials of biological systems is usually made at pH levels other than $pH = 0$, it is necessary to modify the term E_o in the above equation in conformity with this practice and with the effect of pH -changes. The observed O-R potential of a given system depends, therefore, not only on the inherent tendency of the system to yield or accept electrons

and on the ratio of the concentration of the oxidant to that of the reductant, but also, quite frequently, on the pH. In the equation

$$E_h = E'_0 + \frac{RT}{nF} \ln \frac{[\text{Oxidant}]}{[\text{Reductant}]}$$

the term E'_0 represents the characteristic potential of the system at the designated pH and its value is equal to that of the observed potential (E_h) at this pH when $[\text{Oxidant}] = [\text{Reductant}]$. Values of E'_0 , measured at pH levels close to neutrality, have been determined for a considerable number of reversible biological systems; they vary from very negative values (e.g. -0.371 v for the system, hypoxanthine \rightleftharpoons xanthine at pH 7.0) to quite positive values (e.g. $+0.255$ v for the system, ferrous cytochrome C \rightleftharpoons ferric cytochrome C at pH 7.0). Lists of such values are recorded by Fischer (1939), by Oppenheimer and Stern (1939) and by Barron (1943b). Systems with more negative potentials are more reducing than those with more positive potentials. The H-electrode with a potential of -0.421 v at pH 7.0 represents a system of great reducing intensity; at the opposite extreme is the oxygen-electrode having a potential of $+0.810$ v at pH 7.0, representing a system of great oxidizing intensity.

It should be emphasized that in order that an oxidizing or a reducing solution may give a definite, stable potential two important conditions must be satisfied. In the first place, the oxidized and reduced forms must both be present in definite amounts; the potential of a pure oxidant or of a pure reductant is meaningless. Secondly, each of the two components must be capable of conversion into the other as the result of an infinitesimally small change in the equilibrium or static potential in one direction or the other. This means that the system must be thermodynamically reversible; only the potentials measured in such systems have any fundamental significance and only such systems play any significant role in the physiological transport of hydrogen and electrons. Reference to the chemical nature of some of the physiologically important transport systems will be made later. Meanwhile it may be stated that of the several systems concerned some are most easily recognized as carriers of H-atoms or of H^+ ions and electrons, whereas others such as cytochrome transport electrons only. In all cases, however, the catalytic role of the carrier systems in the respiratory process depends on the exchange of electrons.

The significance of O-R potentials in studies of the mechanisms of biological oxidation is twofold. In the first place, knowledge of the characteristic potentials of the several systems which take part in the transfer of electrons from the metabolites to molecular oxygen permits an evaluation of the possibility of reaction between two given systems and provides information as to the sequence in which the several systems may co-operate in electron-transfer. Under suitable condi-

tions it is possible that a system with a more negative potential will reduce a system having a more positive or higher potential. While it cannot be said that a system of higher potential will always oxidize a system of lower potential, a system of lower potential will not oxidize one of higher potential. The sequence of the interaction of the several O-R systems which constitute the respiratory mechanisms of living organisms is probably determined by many factors, one of which—obviously an important one—is the relationship existing between the characteristic potentials of the different reversible systems. But the fact that two O-R systems react with each other *in vitro* does not necessarily mean that they will also react *in vivo*. Considerations of this kind may impose serious limitations on the interpretation of the results of *in vitro* experiments in terms of intracellular reactions. Knowledge of the potentials of reacting systems has also been used in calculating the amount of free energy liberated at successive stages of the respiratory process. Suppose that a system of higher potential is reduced *in vitro* by one of lower potential, and that the difference between their characteristic potentials (E'_0), referred to the normal hydrogen electrode, is E (expressed in volts) when each system is half reduced (or oxidized). The free energy change ($-\Delta F$) is calculated from the equation $-\Delta F = nEF$, where n is the number of electrons transferred and F is the faraday (i.e. approx. 23060 calories).

Dehydrogenases. A dehydrogenase catalyzes the oxidation of a specific metabolite (AH_2) by causing it to give up hydrogen (or H^+ ions and electrons) to a suitable H-acceptor (B) which, thereby, becomes reduced: $AH_2 + B \rightarrow A + BH_2$. Many dehydrogenases have been shown to catalyze reactions which are thermodynamically reversible and which, as *isolated* reactions, can be represented by the following equilibrium:

reduced substrate \rightleftharpoons oxidized substrate + $2H^+ + 2e^-$. The enzyme not only activates the reduced form (AH_2) of the substrate as a H-donor, but it also activates the oxidized form (A) as a H-acceptor. A dehydrogenase-system represented by the equilibrium above is an oxidation-reduction system characterized by a definite O-R potential (E'_0), measurable *in vitro*, which depends upon the chemical nature of the two components and upon other factors such as pH. But the equilibrium is stable only if the ratio of the two components remains unchanged. It is unlikely that such an equilibrium can exist in the living cell because of the presence of other O-R systems, of lower or higher potential, which tend continuously to disturb the equilibrium by donating or accepting electrons.

Dehydrogenation of the reduced component (AH_2) of a reversible dehydrogenase-system can take place only if there is also present another O-R system of higher, more positive, potential, so that its oxidized component (B) can accept hydrogen or electrons from the reduced form of the first system. The reaction of

the two systems with each other is reversible and, in the absence of disturbing factors, will reach a dynamic equilibrium: $A H_2 + B \rightleftharpoons A + B H_2$, with the result that the oxidation of $A H_2$ is far from complete. The process of dehydrogenation of $A H_2$ can go to completion only if $B H_2$ can become a H-donor for another acceptor which is the oxidized component of an O-R system whose potential is higher than that of system B. In this way, through the mediation (as H^+ ion- and electron-carriers) of a series of O-R systems of gradually increasing potential (i.e. having increasing oxidizing intensities), the equilibrium, above, is constantly shifted to the right and the dehydrogenation of $A H_2$ progresses. Eventually the system represented by molecular oxygen, having a very high potential, comes into play and the transfer of hydrogen ions and electrons from the metabolite to O_2 is completed by a virtually irreversible series of reactions in which all of the free energy of the hydrogen is released. In such a series of reactions this energy is liberated in a step-wise manner and energy is made available to the cell at each step in an amount which depends on the difference of potential between the two systems which react with each other at that step. The total energy released in the several steps is equivalent to the energy liberated by the direct oxidation of the hydrogen to water by molecular oxygen.

On the basis of present knowledge of their activities most of the known dehydrogenases can be classified tentatively according to the method of disposal of the hydrogen which is liberated from the substrate as the result of the catalytic action. Several such methods are now recognized.

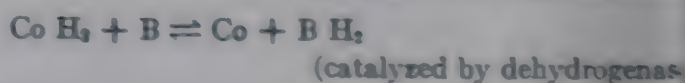
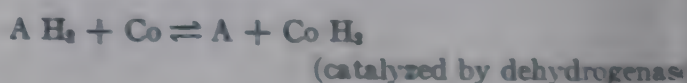
(1) The hydrogen is transferred directly to molecular oxygen, to form H_2O_2 , by a prosthetic group attached to the enzyme protein, as in the case of certain flavo-proteins such as d-amino acid oxidase and xanthine oxidase. The peroxide formed in the reaction is subsequently removed by catalase or, possibly, by peroxidase. Water is the final product.

(2) The hydrogen is oxidized to water through the direct mediation of the cytochrome system between the dehydrogenase system on the one hand and molecular oxygen on the other. It has been customary to include among the dehydrogenases reacting in this manner a few enzymes such as succinic dehydrogenase, lactic dehydrogenase of yeast, α -l(+)-glycerophosphate dehydrogenase of muscle, and two or three others. But in the case of succinic dehydrogenase it now appears that an additional mediator, possibly a flavo-protein, may intervene between the dehydrogenase and cytochrome.

(3) The hydrogen is transferred to molecular oxygen, to form water, through the mediation of a more complex series of oxidation-reduction systems, including one of the two co-dehydrogenases (coenzymes, pyridine nucleotides), a flavoprotein, cytochrome, and cytochrome oxidase, functioning in the order named. Dehydrogenases reacting in this manner are more

numerous than all other types and are further differentiated, according to the nature of the necessary pyridine nucleotide, into three groups: (a) those which require diphosphopyridine nucleotide (coenzyme I), (b) those which require triphosphopyridine nucleotide (coenzyme II), (c) one or two dehydrogenases which exhibit no specificity with respect to the pyridine nucleotide. Members of group (a) are considerably more numerous than those of the other groups. Schlenk (1942) has listed a number of these dehydrogenases together with their essential coenzymes.

In aerobic (respiratory) systems the hydrogen liberated from certain metabolites can be regarded as being transported in one direction to molecular oxygen by one or other of the above methods or by some similar method. The results are: (1) the metabolite is oxidized by the removal of hydrogen, and (2) the hydrogen is oxidized by union with oxygen. In glycolytic systems where anaerobic conditions prevail or where the supply of oxygen is insufficient to enable the respiratory processes to meet the demands of the cell for energy, the hydrogen released from the metabolite is not oxidized by molecular oxygen but may instead, be taken up by another, different, metabolite which is activated as a hydrogen-acceptor by its own specific dehydrogenase and thus becomes reduced. This means that two different dehydrogenase systems each containing an enzyme and its specific substrate react with each other in such a manner that the reduced component ($A H_2$, below) of one system is oxidized to the oxidized component (A) while the oxidized component (B) of the other, while the latter is, of course, reduced to $B H_2$. Linked reactions of this kind have been demonstrated *in vitro* in the presence of one of the pyridine nucleotides (Co) which functions in the transfer of hydrogen, as illustrated by the following equations:

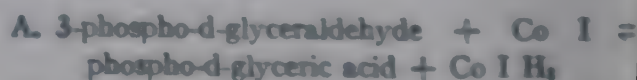


The net result is expressed as follows:

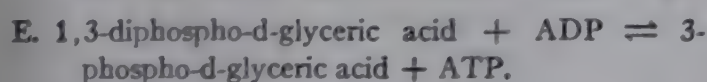
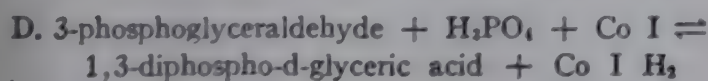


In anaerobic glycolysis, and in fermentation in general, the oxidation of one compound is always accompanied by the reduction of another. Molecular oxygen does not, of course, take part in the reaction.

An important example of a coenzyme-linked reaction is the reduction of pyruvic acid by phosphoglyceraldehyde to form lactic acid, the end product of glycolysis in muscle.



Reaction C is a summation of reactions A and B but it is enabled to proceed only through the mediation of the coenzyme which functions as an oxidation-reduction system in the transfer of hydrogen. [It should be stated that reaction A, as written above, is a simplification of the following reactions, D and E, in which 1,3-diphospho-d-glyceric acid is first formed and is later dephosphorylated enzymatically in the presence of adenosine diphosphate (ADP), to yield 3-phospho-d-glyceric acid and adenosine triphosphate (ATP).



Reaction D is the oxidative (or, more accurately, the oxido-reduction) reaction of alcoholic fermentation and of glycolysis in which an *energy-rich phosphate bond*, in this case a carboxyl phosphate bond, is created in position 1 of 1,3-diphospho-d-glyceric acid. The latter compound serves as a donor of phosphate and energy in reaction E for the replenishment of the reservoir of ATP which is needed for the formation of hexosediphosphate in an earlier stage of glycolysis. An examination of reaction D reveals the fact that it is, in reality, a coupled oxidation—phosphorylation in which an energy-rich carboxyl phosphate (acyl phosphate) is formed from an aldehyde group. The enzymes catalyzing reactions D and E are, respectively, phosphoglyceraldehyde (or triose) dehydrogenase and transphosphorylase; both enzymes have recently been prepared in the form of crystalline proteins, but in each case the crystalline protein can exercise its catalytic activity only in the presence of its specific coenzyme, namely Co I in the first case and adenosine polyphosphate in the second.]

In addition to the H-transporting systems mentioned above, it is not unlikely that other reversible O-R systems may function in a similar manner. To two such systems, namely, oxaloacetate \rightleftharpoons malate (catalyzed by malic dehydrogenase) and fumarate \rightleftharpoons succinate (catalyzed by succinic dehydrogenase) Szent-Györgyi has attributed a pre-eminent rôle in transporting hydrogen from cellular metabolites to cytochrome, and he has suggested that the essential function of the four-carbon dicarboxylic acids in the tissues is to act in this catalytic manner. Space does not permit a discussion of the physiological significance of these compounds; an appraisal of their importance is to be found in the recent review of Krebs (1943).

Cytochrome and cytochrome oxidase. Let us turn now from the dehydrogenases, which can be regarded as functioning at one end of the respiratory chain, to the O-R systems at the other end which are concerned with making molecular, inactive, oxygen available to the cell for the oxidation of hydrogen liberated from cellular metabolites. These latter systems constitute the cytochrome system consisting of the enzyme cytochrome oxidase and three hemochromogen-

like pigments, cytochromes a, b, and c. Each of these four compounds is believed to be a reversibly oxidizable protein-complex containing an iron-porphyrin as its prosthetic group, oxidation and reduction being effected, in each case, by the exchange of an electron of the iron atom ($\text{Fe}^{++} \rightleftharpoons \text{Fe}^{+++} + e$). The discovery of the tetrapyrrol grouping in the structures of these compounds has served further to emphasize its special biological importance; for it is present also in chlorophyll (in which magnesium replaces iron), in hemoglobin, in catalase, in peroxidase and in other compounds of physiological significance. The tetrapyrrol structure appears, therefore, to be necessary not only for securing solar energy to be used in biological activities of all kinds, and for transporting molecular oxygen from the lungs to the tissues of higher animals, but also for its utilization in energy-liberating reactions within the tissues themselves.

Warburg was the first to realize the importance of the iron-porphyrin structure in intracellular oxidation. Since a large proportion, sometimes 90 per cent or more, of the normal oxygen-consumption of cells of many types can be blocked by small amounts of cyanide, Warburg was led, several years ago, to suspect that the enzyme chiefly responsible for the catalysis of oxygen-consumption in aerobic cells is a compound containing a heavy metal such as iron. Later, when he observed that the oxygen-consumption of the cells was greatly diminished in the presence of carbon monoxide if the system was kept in the dark, but that respiration was not affected by CO when the cell-suspension was exposed to light, he suggested that the enzyme is a conjugated protein whose prosthetic group is an iron-porphyrin; for the only substances known to form light-dissociable compounds with CO are those which contain an iron-porphyrin as a part of their structure. Still later, by means of an ingenious photochemical method, Warburg was able to obtain, as he believed, an accurate picture of the absorption-spectrum of the CO-compound of the enzyme, without even attempting to remove the enzyme from the cells. The spectrum so obtained resembled very closely the spectra of the CO-compounds of several heme-containing substances such as pyridine- and nicotine-hemochromogens; these latter spectra were determined not only by the conventional methods but also by the same photochemical procedure as had been employed with cell-suspensions. It is not possible, in this short section, to include a description of Warburg's experimental procedures and observations; nor is it necessary to consider the theoretical aspects of his interpretations. He was, however, led to the definite conclusion that the enzyme concerned with cyanide-sensitive respiration in living cells is an iron-porphyrin-protein complex; in spite of subsequent criticism of his methods and interpretations, his conclusion as to the chemical nature of the enzyme has never been seriously challenged.

To this enzyme Warburg gave the name "the oxygen-transferring enzyme"; and, in the early formulations

of his ideas as to its mode of action, he attributed to it the function of "oxygen-activation," as a result of which oxygen is enabled to oxidize directly the metabolites of the cell. This conception differed fundamentally from that of Wieland which emphasized the dominant role of the dehydrogenases as the activating agents responsible for the consumption of oxygen. Wieland regarded the liberated, "activated" hydrogen as undergoing direct oxidation by molecular oxygen.

As a result of experiments initiated some twenty years ago by Keilin, it became clear that neither the dehydrogenase systems, alone, nor an agent of the type of Warburg's enzyme, alone, can catalyze the oxidation of cellular metabolites by molecular oxygen. Keilin showed that both types of catalyst are essential components of a more complex oxidative system than that postulated either by Warburg or by Wieland. In 1886 MacMunn had observed in muscle and other tissues certain pigments which he named myo- and histo-hematin; until 1925, however, they had failed to arouse any widespread interest. In that year Keilin announced the discovery of three heme-containing pigments, in aerobic cells and tissues of many kinds, to which he gave the names cytochrome a, b, and c; the c-component appeared to correspond, spectroscopically, to the modified pigment of MacMunn. These pigments were later shown by Keilin to function as mediators linking the dehydrogenase systems of the cell with the system composed of molecular oxygen (O_2) and an enzyme, formerly known as indophenol oxidase but now generally recognized as cytochrome oxidase. This enzyme resembles very closely Warburg's "oxygen-transferring enzyme"; but, instead of oxidizing directly a large number of cellular compounds, in the manner suggested by Warburg, it is restricted in its action to the oxidation of the ferrous iron of one of the cytochromes by O_2 .

The three pigments together with cytochrome oxidase constitute a system which transports electrons to O_2 , and, by doing so, makes possible the oxidation of the hydrogen liberated from cellular compounds which are activated by specific dehydrogenases. Though all four components of the cytochrome system are believed to be iron-porphyrin-protein compounds, the oxidase differs from the cytochromes in several respects. For example, though the oxidase reacts directly with O_2 , cytochromes a and c are not autooxidizable except in the extreme ranges of pH; cytochrome b reacts directly with O_2 and, to some extent therefore, may be independent of the oxidase. Moreover, cytochrome oxidase in its ferrous form combines with CO to form a light-dissociable compound, and in its ferric form with cyanide; as a result of either combination, the activity of the enzyme is inhibited, apparently by interference with the transfer of electrons. On the other hand, the positions of the characteristic absorption bands of all three cytochromes are unaffected by the presence of either CO or cyanide, an observation which has been interpreted to mean that none of the three cytochromes combines with either CO or cyanide

(Keilin and Hartree (1939)). But since each of these substances can inhibit respiration in cells which contain cytochrome, it is concluded that the cytochromes themselves must function only as systems which transfer electrons between cytochrome oxidase on the one hand, and, on the other, the dehydrogenase itself, as in the case of dehydrogenases of class 2, or a flavoprotein, as in the case of dehydrogenases of class 3. Two other cytochromes, a_3 and b_2 , have been described, but their properties and functions will not be discussed here.

Upon their release from the metabolites, or more usually from a flavoprotein which has served as an intermediary hydrogen-carrier, the "metabolic" hydrogen-atoms are ionized and yield H-ions. The electron lost by each H-atom is believed to be taken up in succession by the trivalent iron of the components of the cytochrome system, in other words by four iron-porphyrin compounds, reducing each in turn ($Fe^{+++} + e \rightleftharpoons Fe^{++}$). Each cytochrome on yielding an electron to the ferric iron of the adjacent member of the chain becomes reoxidized and is then in a position to accept another electron. Finally, the divalent iron of the oxidase itself, the last member of the series, is oxidized to the trivalent state by O_2 . The mechanism of this oxidation is still only imperfectly understood; without attempting to discuss the theoretical aspects of the problem, it is sufficient to state that the interaction of O_2 and the ferrous form of cytochrome oxidase in an aqueous medium facilitates the transport of electrons by the cytochrome system as a whole and makes possible the oxidation of metabolic hydrogen to water. It is unlikely that all four compounds necessarily function in the cyanide-sensitive respiration of aerobic cells of all types, since some types of cells are known to lack one or other of the three cytochromes. The sequence in which the four compounds participate in the transfer of electrons to O_2 is believed to be as follows: cytochrome b—cytochrome c—cytochrome a—cytochrome oxidase. This conclusion is based upon considerations of the O-R potentials of the several systems.

Only one of the pigments, namely cytochrome c, has been obtained in soluble form; the others are so intimately bound to the insoluble material of the cells that they have resisted all attempts to separate them from this material. The c-component has, however, been highly purified. The purest preparation obtained by Theorell had a heme-iron content of 0.43 per cent and molecular weight of 13000. The structure and amino acid content of this product have been described by Theorell and Åkesson (1941). It is of considerable interest that approximately 30 per cent of the total nitrogen (including the porphyrin nitrogen) of cytochrome c is represented by the essential amino acid lysine, a compound which has not yet been identified with any specific reaction or function in living organisms. No other protein is known to contain such a large proportion of lysine.

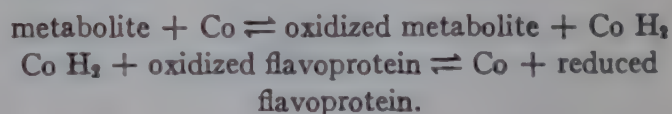
Until quite recently no one had succeeded in obtain-

ing a clear solution of cytochrome oxidase free from insoluble cellular particles. Using procedures such as high-speed centrifugation and ultrasonic radiation, Haas (1943) obtained from pig-heart a water soluble preparation with a slight Tyndall effect, containing an enzyme, having cytochrome oxidase activity, whose properties, like those of indophenol oxidase, appeared to be identical, in several respects, with those of Warburg's enzyme. In later studies, Haas (1944) separated the enzyme into two fractions, one of which proved to be more heat-stable and more soluble than the other; both components were found to be necessary for the oxidation of cytochrome c by molecular oxygen.

The pyridine nucleotides and flavoproteins. Reference has been made to the fact that many dehydrogenases depend for their activity upon the co-operation of a coenzyme which is either diphosphopyridine nucleotide (cozymase, coenzyme I) or triphosphopyridine nucleotide (coenzyme II). The coenzyme is regarded by some workers as a prosthetic group bound to a specific activating protein or "apodehydrogenase," the two components together forming a "pyridinoprotein" having the properties of a specific dehydrogenase. Others prefer to look upon the activating protein itself as the dehydrogenase and the coenzyme as one of its substrates. At the moment of catalysis the metabolite and the coenzyme are both bound to the activating protein, and hydrogen is transferred from the metabolite to the coenzyme, with the result that the former is oxidized and the latter reduced. Unless, however, the reduced coenzyme can be reoxidized, the extent of oxidation of the metabolite is negligible since it is limited by the small amount of coenzyme present. One method of reoxidation of the coenzyme, as in coenzyme-linked oxidation-reduction reactions, has already been mentioned. A second method is of greater significance in respiration and is concerned with the catalytic role of certain flavoproteins which oxidize the reduced coenzyme by transferring its labile hydrogen to O_2 by way of the cytochrome system in the manner already described. The coenzymes themselves do not react directly with O_2 ; the only known physiological agents which can effect their oxidation by O_2 , *in vitro*, at adequate speeds are two specific flavoproteins. One of these, known as cytochrome c-reductase (CR) and found, so far, only in yeast, is a dehydrogenase which specifically catalyzes the oxidation of reduced coenzyme II ($Co II H_2$) by oxidized cytochrome c. In this way CR may link the cytochrome system with the dehydrogenase systems which depend upon $Co II$. The other flavoprotein, named diaphorase or coenzyme-factor, is present in animal tissues as well as in yeast and bacteria and has been shown to catalyze the oxidation of $Co I H_2$ (and possibly $Co II H_2$) by methylene blue *in vitro*. In an aerobic system the resultant leucomethylene blue is reoxidized by O_2 , so that a relatively small amount of the dye enables the physiological carriers to transport relatively large amounts of metabolic hydrogen to O_2 . The direct reaction of diaphorase with the cytochrome

system has not been satisfactorily demonstrated; however, the facts that diaphorase can oxidize $Co I H_2$ and that the oxidation, in tissue slices, of the substrates of several dehydrogenases which require $Co I$, is sensitive to cyanide, suggest that diaphorase constitutes at least part of the link between $Co I H_2$ and the cytochrome system. The nature of the other part of the link is still unknown. Straub in 1939 obtained from pig-heart a soluble flavoprotein having all the catalytic properties of the coenzyme-factor, the activity of which had hitherto been associated with insoluble particles in the tissue extracts. The activity of Straub's flavoprotein was such that under optimum conditions each molecule of the enzyme catalyzed the aerobic oxidation of ca. 8000 molecules of $Co I H_2$ per minute by carriers such as methylene blue. Since this flavoprotein also oxidizes $Co II H_2$, it may be the factor which is mainly concerned with the oxidation of both coenzymes in animal tissues. But the reaction of the reduced flavoprotein with the cytochrome system under physiological conditions still awaits further clarification.

The reactions involving the dehydrogenase, the pyridine nucleotide and the flavoprotein can be summarized as follows:



The reduced flavoprotein (i.e. either diaphorase or CR) is eventually reoxidized by oxidized cytochrome; in the case of CR this oxidation appears to be effected directly by oxidized cytochrome c, whereas in the case of diaphorase another carrier, as yet unknown, may intervene between the flavoprotein and the cytochrome system. The oxidation of the hydrogen transported by the flavoprotein is, eventually, made possible by the mediation of the cytochrome system in the manner previously described. The oxidation product is water.

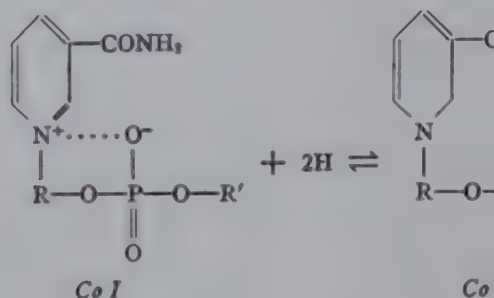
Only a brief reference to the chemical nature of the coenzymes and flavoproteins is possible here. Both pyridine nucleotides (coenzymes) are, in reality, dinucleotides containing two mononucleotides united through their phosphoric acid residues. $Co II$ contains a third phosphoric acid residue but is, otherwise, similar in structure to $Co I$. One of the mononucleotides in each coenzyme is adenylic acid (adenosine-5'-phosphate); the other mononucleotide contains nicotinic acid amide, d-ribose and phosphoric acid united in this order (i.e. nicotinamide-d-riboside-5'-phosphate). The flavoproteins are compounds in which a specific activating protein is bound to a prosthetic group which may be either a mononucleotide, flavin phosphate, (i.e. the 5'-phosphate of 6, 7-dimethyl, 9-d-ribityl isoalloxazine) as in cytochrome c-reductase, or a dinucleotide, flavin-adenine dinucleotide, containing flavin phosphate and adenylic acid united through their phosphoric acid residues. The dinucleotide is present in a number of flavoproteins, including diaphorase.

The following reactions illustrate the manner in which hydrogen, released from cellular metabolites through the agency of specific dehydrogenases, is transferred to diaphorase by way of coenzyme I.

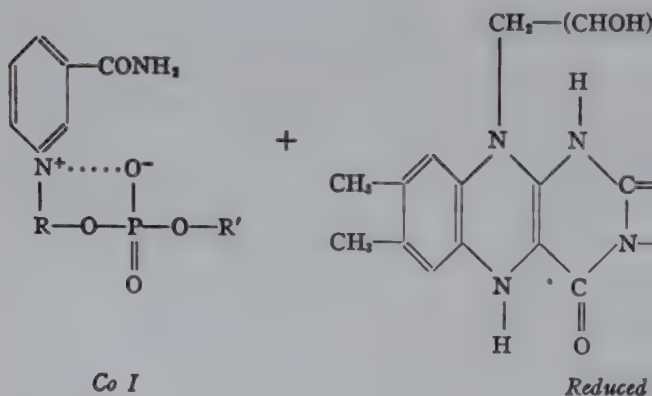
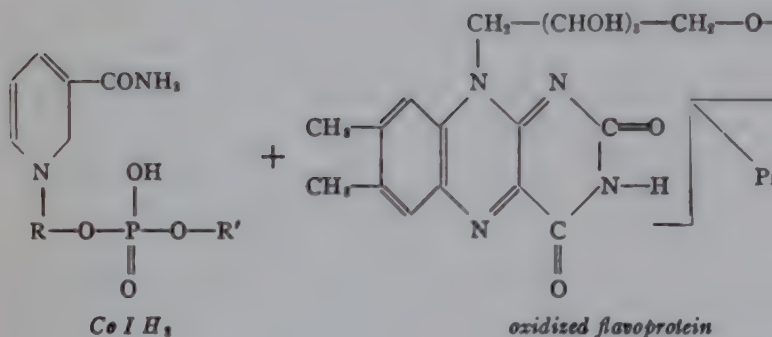
and the final re-
water

In addition
pyridine nucle

A.



B.



R = residue of d-ribose.

R' = residue of adenylic acid.

be oxidized by a flavoprotein which Green (1944) has shown to be present in rat-kidney. It is generally believed that the flavoprotein oxidases which react directly with molecular oxygen are responsible for a large proportion of the cyanide-insensitive respiration of aerobic cells. The yellow enzyme of Warburg and Christian, 1932, has the distinction of being the first flavoprotein to have been isolated from living cells (yeast) but no significant physiological role has, as yet, been attributed to it; indeed, there is reason for believing that this product, now known as the "old yellow enzyme" may have resulted, during its extraction from yeast, from the denaturation of some other flavoprotein such as cytochrome c-reductase. In any event, no one has succeeded in demonstrating the presence of any flavoprotein in animal tissues which is identical with Warburg and Christian's yellow enzyme.

The preceding brief description of some of the oxidative catalysts of living organisms does not, of course, embrace all oxidases which are believed to exist in living cells. But the oxidation systems which have been discussed appear to constitute a recurring pattern in organisms of widely different types. These respiratory enzyme systems are made up of two main components: (1) a specific catalytic protein whose function is concerned with the release of H-atoms from the oxidizable substrate, (2) a number of reversible oxidation-reduction systems which transport either the hydrogen atoms themselves or electrons which are derived from them, from the substrate to molecular oxygen. The potentials of these systems become more positive as the oxygen-end of the respiratory chain is approached. In some cases only a single O-R system intervenes between the substrate and O_2 , as in the oxidation of α -amino acids by a specific flavoprotein. In other cases two different O-R systems function as carriers, as for example in the oxidation of succinic acid by succinate dehydrogenase, in which an unknown carrier and the cytochrome system are concerned. In still more complicated respiratory systems at least three different types of O-R systems may take part in the transport of hydrogen and electrons, namely, one of the pyridine nucleotides, a flavoprotein, and the cytochrome system. The transport of hydrogen by the pyridine nucleotide and by the flavoprotein in such a system is frequently formulated as a bivalent process, two H-atoms being transferred simultaneously. But the investigations of Michaelis and his co-workers [see Michaelis, 1940] have indicated that every oxidation or reduction is step-wise in character; in each step one electron is transferred, the intermediary substance formed in the first step of a bivalent reaction being a free radical, a semi-oxidized or semi-reduced form. When applied to dehydrogenase reactions in biological systems this principle of free radical formation is of particular interest; for it provides an explanation of the manner in which an apparently bivalent reaction can be linked with the univalent transfer of electrons by the cytochrome system. At each step along the respiratory

path leading from the metabolite to O_2 free energy may be made available to the cell, the amount of energy depending upon the relative oxidation-reduction potentials of the adjacent O-R systems which react with each other in the transport of electrons. Ball (1944) has made some calculations of the possible free energy released in the successive steps. Of the total free energy liberated during the passage of one electron from the pyridine nucleotide to O_2 by way of flavoprotein and the cytochrome system, approximately 75 per cent is liberated during the passage of the electron through the cytochrome system to O_2 .

Other oxidases. Some plants and certain lower forms of animal life contain oxidases which are copper-protein compounds and do not, therefore, fall into any of the special categories discussed in this chapter, though their activity is, in some respects, similar to that of dehydrogenases in general. They catalyze the direct oxidation of their substrates by molecular oxygen, the copper of the enzyme acting as a prosthetic group in the transfer of electrons from the substrate to O_2 . The copper-containing enzymes include those which oxidize ascorbic acid, mono- and polyphenols. Higher animals do not appear to possess enzymes of this kind.

Unclassified oxidases include, among others, the enzymes uricase, which oxidizes uric acid to allantoin; amine oxidase; diamine oxidase, which oxidizes certain diamines and histamine with the liberation of ammonia and the formation of an aldehyde and H_2O_2 ; luciferase, which is concerned with the phenomenon of luminescence in luminous bacteria and other organisms; fatty acid dehydrogenase which is present in the liver and muscle of the rat and oxidizes certain higher fatty acids.

Glutathione. This tripeptide, glutamyl cysteinyl glycine, discovered in 1921 by Hopkins, is almost universally distributed in the intracellular fluids of animal tissues as well as in plants, yeasts and many bacteria. Of all the known cellular compounds containing the sulphhydryl group, apart from the proteins, glutathione is probably the most widely distributed in living cells; for this reason and because it is capable of reversible oxidation to the disulphide form, many attempts have been made to demonstrate its activity as a hydrogen-transporting system in cellular oxidations. It is doubtful, however, whether such a function can be attributed to the compound; for all attempts to demonstrate the full reversibility of the change from the reduced (sulphydryl) form to the oxidized (disulphide) form have failed. The potential of the system appears to be determined solely by the reduced form; it is unlikely that a substance having these properties can play any important role in the physiological transport of hydrogen or electrons in respiratory systems. Moreover, the fact that it is present in living cells almost entirely in the reduced form suggests either that the reduction of its oxidized form is much more rapid than the oxidation of its

reduced form, or that there is no cycle of reduction and oxidation.

Other functions of glutathione have, however, been more firmly established. It acts, for example, as a coenzyme in the transformation of methyl glyoxal to lactic acid by the enzyme glyoxalase. But, in the present discussion, its role in maintaining the —SH groups of enzymes is of greater interest. The presence of the sulphhydryl group in several oxidizing enzymes, as well as in several proteolytic and other enzymes, has been shown to be necessary for their activity (Bersin 1935, Hellerman 1937, Barron and Singer 1945). In view of the fact that oxidizing agents in the cell tend to inhibit the activity of —SH enzymes, it is probable that one of the main functions of glutathione in cellular systems is concerned with the continuous reactivation of the —SH enzymes. Its capacity to bring about such a reactivation, through its powerful reducing action, has been demonstrated in many experiments. Glutathione appears, therefore, to influence cellular oxidations in an indirect rather than in a direct manner.

It must be emphasized that much of our knowledge of the oxidizing systems present in living organisms has been acquired in studies of the activity of extracts and of "reconstructed" systems of many kinds. But the ultimate aim is an understanding of reactions and processes in the living, undamaged cell, an organized, heterogenous structure of great complexity. Studies of reconstructed systems representing fragments of cellular structures cannot possibly reveal the full significance of cellular organization in relation to metabolic processes.

Relation of vitamins to oxidative catalysts. At least three water-soluble vitamins bear a close relationship to intracellular oxidative catalysts. Nicotinic acid in the form of its amide is a constituent of the pyridine nucleotides, and riboflavin enters into the structure of the flavoproteins; these two vitamins appear, therefore, to be necessary for the formation of compounds which are primarily concerned with the transport of hydrogen from cellular metabolites to O_2 . A third vitamin, thiamin, is believed to function in the cell, in the form of thiamin pyrophosphate, as a coenzyme in the enzymic transformation of α -keto acids such as pyruvic and α -keto-glutaric acids, in reactions involving decarboxylation, oxidation, condensation, CO_2 -fixation, dismutation. The role of thiamin pyrophosphate (co-carboxylase) in intermediary metabolism has been discussed in several recent reviews, including those of Ochoa (1942) and Barron (1943a).

The liberation of CO_2 in decarboxylation reactions accounts for a large proportion of the CO_2 formed during the oxidation of carbohydrates; similar reactions are probably responsible for the formation of CO_2 during the oxidation of fatty acids, though the pathways by which fatty acids are oxidized have been less thoroughly explored. Decarboxylations, in general, are not accompanied by any appreciable energy-change;

the energy liberated in biological oxidations is believed to originate very largely in the oxidation of hydrogen. Decarboxylation is, nevertheless, an important reaction; for it reduces the size of the carbon-skeleton of a compound and, in this way, creates a new molecular species which can be activated by its own specific oxidase.

The relation of other vitamins to oxidative reactions in animal tissues is much less firmly established than is that of the three vitamins mentioned above. The reversible oxidation of ascorbic acid *in vitro* and the unsaturated nature of the molecule of vitamin A suggest that these vitamins may play some part in oxidative reactions *in vivo*, but in neither case is there any convincing experimental evidence of such a role in animal tissues. On the other hand, recent studies have indicated that vitamin E is related in some manner to the oxidative systems of skeletal muscle. Houchin and Mattill (1942) have observed that dystrophic muscle removed from vitamin E-deficient animals, as compared with muscle from normal animals, has a considerably higher respiration *in vitro*, as measured by oxygen-consumption. Biopsy experiments on the E-deficient rabbit demonstrated that the oral administration of α -tocopherol or the parenteral administration of tocopherol phosphate lowered the high initial respiration of the muscle toward normal values. In other experiments, the *in vitro* respiration of dystrophic muscle-slices was significantly lowered by α -tocopherol phosphate added to the medium; the succinic acid oxidase activity of dystrophic muscle, *in vitro*, was similarly reduced by added α -tocopherol phosphate. Tocopherol itself had no effect in either case. The full significance of these results is not yet clear; while they suggest, as Houchin points out, that tocopherol phosphate acts as a "brake" on the oxidative mechanisms of skeletal muscle, nothing is known of the manner in which the effect is exercised.

The coupling between oxidation and phosphorylation in biological systems. Recent studies of the coupling of oxidation with phosphorylation have assisted greatly in explaining at least one mechanism by which energy liberated in oxidative reactions can be stored temporarily for subsequent utilization by the organism. Equation D on page 327 represents a reaction in which the aldehyde group of 3-phosphoglyceraldehyde is oxidized to a carboxyl group while, at the same time, an acyl phosphate, namely 1,3-diphosphoglyceric acid is formed. In this oxido-reduction step, sometimes called the oxidative reaction of glycolysis (see fig. 150 $\frac{1}{2}$)*, inorganic phosphate enters into the formation

* The writer is greatly indebted to Dr. V. R. Potter for permission to reproduce this figure from his paper, published in 1944, on "Biological Energy Transformations and the Cancer Problem." Commenting on this figure, Potter (1944) states in part: "The metabolism of any given tissue is the resultant of the balance between the various enzymes that are responsible for

of an energy-rich phosphate bond as the result of an oxidative (energy-yielding) process. Potential energy is thus accumulated. [Ordinary phosphoric acid ester linkages, as in glycerophosphate, involve only a relatively small energy-change (3000 calories or less), in contrast with *energy-rich linkages* where the energy-change is of the order of magnitude of 8000 to 12000 calories. Linkages of the latter type occur in adenosine di- and tri-phosphates, creatine phosphate, arginine phosphate, phosphopyruvic acid, and acyl phosphates.] The change in free energy (ΔF) in going from carbonyl (aldehyde) to carboxylate (acid) at pH 7 is stated by Kalckar (1944) to be -29000 calories. Of this amount, $+12500$ calories are used for the coupled reduction of Co I to Co I H_2 (equation D); the remaining -16500 calories are available for synthesis (i.e. the creation of an energy-rich phosphate bond at position 1), approximately -11000 calories being stored as unstable acyl

O
||
R—C—O—PO₃H₂

phosphate (R—C—O—PO₃H₂) in 1, 3, diphosphoglyceric acid (DPG). In reaction E on page 327 (see also fig. 150½) DPG reacts with adenosine diphosphate (ADP) to form 3-monophosphoglyceric acid and adenosine triphosphate (ATP). In this reaction an energy-rich phosphate bond is transferred, by a specific transphosphorylase and without dissipation of energy (ca. 11000 calories), from position 1 in DPG to its new position in ATP. This reaction is one of two reactions, in the glycolytic series, which serve to replenish the store of phosphate-bond energy in ATP. As Meyerhof (1944) points out, the phosphorylation of ADP to ATP in this reaction represents a net gain in free energy, while the Co I H_2 (produced in reaction D, page 327) is reoxidized in the reduction of one mole of pyruvic to lactic acid (reaction B, page 326). The second glycolytic reaction in which an energy-rich phosphate bond is formed in ATP is the reaction between phosphoenolpyruvic acid and ADP to yield pyruvic acid and ATP. The formation of the energy-rich phosphate bond in phosphopyruvic acid is the result of an intramolecular change from 3-phosphoglyceric acid to 2-phosphoglyceric acid, followed by dehydration to yield 2-phosphoenolpyruvic acid. Lipmann (1941) has calculated the ΔF of the reaction, phosphoenolpyruvate + H_2O = pyruvate + phosphate, to be 11250 calories. This amount of energy is sufficient to create an energy-rich phosphate bond in ATP when phosphoenolpyruvate reacts with ADP. [This latter reaction, unlike all the other reactions encountered in the transformation of glycogen into lactic acid, has, until very recently, been considered to be irreversible and is indicated as such in figure 150½.]

each of the reactions in the figure. Certain of the starting materials which are stored in the cells or must be brought to the cells are shown at the periphery of the figure. These materials include glucose, oxygen, glycogen, fat and various vitamins which serve as building blocks for coenzymes."

However, Lardy and Ziegler (1945) have demonstrated that the reaction is reversible, provided that K^+ ions are present.]

Thus, in two reactions of the glycolytic series, the store of ATP is replenished; this is, of course, desirable and necessary because the ATP reserve is depleted in earlier reactions of glycolysis which lead to the formation of fructose-1-6-diphosphate.

The formation of energy-rich phosphate bonds has also been shown to take place as the result of the coupling of phosphorylation with aerobic oxidations. For example, Lipmann (1942) isolated acetyl phosphate, the primary product of the oxidation of pyruvate, by *Lactobacillus Delbrückii*, to CO_2 and acetate. Acetyl phosphate contains an energy-rich phosphate bond which can phosphorylate adenylic acid to form ATP. Moreover, Umbreit and others (1942, 1943) have made the interesting observation that the autotrophic sulphur bacillus, *Thiobacillus thio-oxidans*, can store the energy of sulphur-oxidation in the form of energy-rich phosphate bonds of ATP, and that this energy can be used anaerobically in the dark for the assimilation of CO_2 in this organism.

Recent investigations have indicated that another source of energy for the formation of energy-rich phosphate bonds in ATP is to be found in the aerobic oxidative cycle of reactions, known as the Krebs or isocitric acid cycle, by which pyruvic acid (or carbohydrate by way of pyruvic acid) is oxidized to CO_2 and water. From figure 150½ it is apparent that one complete cycle liberates 3 moles of CO_2 , representing the oxidation of all three carbon atoms of pyruvic acid; 5 pairs of H-atoms are also liberated in the cycle and are ultimately oxidized via the cytochrome system to yield water and energy. From the recent work of Ochoa (1943) it now appears that part of this energy (ca. 60 per cent) is used to form energy-rich phosphate bonds. He calculated that for each of the 5 atoms of oxygen consumed in the oxidation of the 5 pairs of H-atoms, 3 moles of inorganic phosphate, on the average, are esterified to form adenosine polyphosphate. In figure 150½ the five groups of triple arrows connecting the Krebs cycle with the ATP system are intended to express this relationship. Ochoa's results, in addition to other evidence, would seem to indicate that during the oxidation of pyruvate in the Krebs cycle, intermediary phosphorylated compounds are formed, containing energy-rich phosphate bonds. But, apart from acetyl phosphate, identified by Lipmann as the primary product in the oxidation of pyruvate (by lactic acid bacteria), no other phosphorylated intermediary compound which could arise in the Krebs cycle has, as yet, been identified. Potter (1944), commenting on figure 150½ which is reproduced from his paper, states: "The figure does not show the exact mechanisms for the aerobic phosphorylations in the Krebs cycle because these are not known, but each of the di- and tricarboxylic acids shown probably occurs in phosphorylated form."

Krebs (1943) has pointed out that some 8 or 9 amino acids can yield, directly or indirectly, either pyruvic acid or oxaloacetic acid or α -keto-glutaric acid. These three acids are intermediaries in the isocitric acid cycle, and, therefore the oxidation of the amino acids from which they can arise is facilitated by the cyclic mechanism. Since the 8 or 9 amino acids may constitute a considerable fraction of some proteins (e.g. 43 per cent of casein), the Krebs cycle may represent an important pathway for the oxidation of protein in some animal tissues; if so, it is to be expected that the oxidation of the amino acid derivatives by way of the cycle will yield phosphate-bond energy to be stored in adenosine polyphosphate.

It is probable that energy-rich phosphate bonds are also formed during the oxidation of lipids. Lardy and others (1945) have shown that the oxidation of the endogenous lipid-reserve of bovine spermatozoa is accompanied by the esterification of inorganic phosphate to form a labile ester which appears to be ATP. This is the first report of the fixation of phosphate during the oxidation of lipids. According to Lehninger (1945), the oxidation of fatty acids by enzymes present in liver-homogenates is activated by ADP or ATP or by a compound which can form ATP by donating phosphate to adenylic acid. He has suggested that preliminary phosphorylation of the carboxyl group of the fatty acid by ADP or ATP to form an acyl phosphate is an obligatory step in the oxidation of the acid, and that at a later stage of oxidation the energy-rich phosphate bonds are returned to the ATP-reservoir.

The utilization of phosphate-bond energy. In the preceding paragraphs some of the metabolic reactions leading to the formation of energy-rich phosphate bonds have been discussed briefly. ATP contains two such bonds, each of which represents an accumulation of ca. 11000 calories; ADP contains one bond of this type. The adenylic system consisting of adenylic acid, ADP and ATP, constitutes a coenzyme whose function appears to be concerned only with trans-phosphorylations but not with the uptake or direct release of inorganic phosphate. On the left-hand side of figure 150 $\frac{1}{2}$ several paths are indicated by which the phosphate-bond energy of ATP is believed to be utilized in the performance of work of different kinds. Various aspects of the problem of the generation and utilization of phosphate-bond energy have been discussed in several recent reviews, including those of Lipmann (1941), Meyerhof (1944), Kalckar (1942, 1944) and Potter (1944).

The relation of ATP to muscular contraction is discussed in another chapter of this book; therefore, only a brief reference to this subject is made here. The breakdown of ATP in muscle was found, several years ago, to be closely associated in point of time with the act of contraction, an observation which led to the suggestion that the energy necessary for contraction is derived directly from ATP. During the past few years this view has gained widespread acceptance.

But the mechanism by which the energy of ATP is made available to the muscle is almost completely unknown. When Engelhardt and Lyubimova discovered, in 1939, that in the myosin fraction, i.e. the contractile element, of muscle there is present in relatively large amounts an enzyme, adenosine triphosphatase (ATP-ase), which liberates inorganic phosphate from ATP (see Engelhardt, 1942), interest in the relationship between ATP and function became intensified. Moreover, the observation of Bailey (1942, 1944) that Ca^{++} ions activate the ATP-ase of myosin (the enzyme apparently hydrolyzing ATP only to the ADP-stage), coupled with observations of others that the stimulation of muscle is accompanied by the release of Ca^{++} ions, would seem to indicate an association between the activity of the enzyme and function. But no proof of such an association has, as yet, been obtained. If the enzyme acts merely as a hydrolytic agent, liberating inorganic phosphate from ATP, the potential energy accumulated in the energy-rich phosphate bond would be dissipated as heat. A more probable mechanism for the utilization of the phosphate-bond energy of ATP in contraction would involve, as a preliminary step, an intermediary coupling of the dephosphorylation of ATP with the phosphorylation of myosin, in order to maintain the phosphate group potential at a high level. So far, however, no experimental evidence of any such transfer of phosphate to myosin has been obtained, though the guanidine group of arginine in the protein would seem to provide a suitable point of attachment of phosphate to form an energy-rich bond. Apart altogether from these considerations, there remains the unsolved problem of the nature of the mechanisms which enable the muscle to transform chemical energy into mechanical work.

If the immediate energy for contraction is, indeed, derived from ATP, the resynthesis of the compound can be effected by the transfer of energy-rich phosphate bonds from creatine phosphate. This compound (CP) serves as a reservoir of phosphate-bond energy and reacts with adenylic acid and with ADP to yield ADP and ATP, respectively. In these reactions phosphate-bond energy is transferred to the adenylic system, and free creatine is formed. For the subsequent resynthesis of CP from creatine, phosphate-bond energy is drawn, in turn, from the ATP reservoir which is maintained at an essentially constant level by the acquisition of phosphate from energy-rich phosphorylated intermediary compounds formed in the glycolytic and oxidative reactions previously discussed. The special value of the reservoir of energy in creatine phosphate is associated with the fact that only by interaction between CP and the adenylic system can the phosphate-bond energy of CP be released; muscle is not known to contain an enzyme which can hydrolyze CP with the formation of free creatine and free phosphate, and therefore it would appear that there is no possibility of the dissipation

of the energy of creatine phosphate by direct hydrolysis. Under conditions of normal energy-requirements, the total reserve of phosphate-bond energy is not depleted, since it is in dynamic equilibrium with the glycolytic and oxidative sources of energy.

Pathways of carbohydrate breakdown and the Pasteur effect. It has been the main purpose of this section to consider, in broad outline, the principal oxidizing enzyme systems of living cells, as understood at the present time, in relation to the liberation and utilization of free energy. No attempt has been made to discuss in detail the intermediary chemical reactions of carbohydrate metabolism. The accompanying figure illustrates mechanisms which have been proposed to explain the degradation of carbohydrate under anaerobic and under aerobic conditions. These and other mechanisms are discussed critically in several recent reviews, including those of Meyerhof (1942), Evans (1942), Dorfman (1943), Krebs (1943) and Barron (1943a), and in recent papers of Sacks (1943, 1944).

Another problem which can only be mentioned here is that of the mechanism of the Pasteur effect. This effect is most accurately defined as the inhibition, by oxygen, of the accumulation of the products of the anaerobic breakdown of carbohydrate in organisms and tissues which are equipped with mechanisms enabling them to release energy from carbohydrate either by fermentation or by oxidation. An example of such a tissue is skeletal muscle which is able to obtain free energy from glycogen either by fermentation (in this case "glycolysis"), with the formation of lactic acid,

or by oxidation to CO_2 and water. Glycolysis appears to be an emergency mechanism which operates when the supply of oxygen is insufficient to enable the respiratory mechanisms to meet the energy-demands of the organism, during, for example, a short period of hard work when a relatively large amount of lactate accumulates in the blood and a correspondingly large oxygen-debt is incurred. Under conditions of prolonged but moderate muscular effort, on the other hand, the anaerobic mechanism appears to operate only during a brief period at the beginning of exercise; during this preliminary period of adjustment the oxygen-consumption rises to a new equilibrium-level which remains relatively constant during the period of moderate work, after which it drops quickly to the resting level. The blood-lactate which had risen slightly, as the result of glycolysis, during the initial period of adaptation returns to nearly normal levels shortly after the attainment of the new equilibrium-level of oxygen-consumption, indicating that as soon as the oxygen supply has become adjusted to the increased demands for energy the anaerobic mechanism no longer operates. In other words, oxygen, when present in adequate amounts, suppresses glycolysis. This is the Pasteur effect. In the case of intensive short-term effort the adaptation is too slow to supply oxygen in adequate amounts and the organism must depend upon the anaerobic mechanism for its supply of free energy. The mechanism of the Pasteur effect is discussed by Dixon (1937), Burk (1939), Johnson (1941), Lipmann (1942).

CHAPTER XXXIII

THE CARRIAGE OF CARBON DIOXIDE BY THE BLOOD

The total carbon dioxide content of blood means the amount of CO_2 which can be extracted from a given volume of blood by exposure to a vacuum after the addition of acid. The results are usually expressed as volumes per cent (v.p.c.) by which is meant cc. of CO_2 (measured at S.T.P.) per 100 cc. of blood. The methods of Van Slyke and his coworkers are now most commonly used for the measurement of CO_2 in blood and other fluids. In Van Slyke's manometric apparatus a known volume of blood is acidified and subjected to a partial vacuum in which CO_2 and other gases are rapidly extracted. The gases are then compressed to a known volume and their pressure measured. The CO_2 is removed by introducing NaOH and the pressure at the same volume is again measured. From the change in pressure the amount of CO_2 can be calculated. By such a method then, it is found that human blood normally contains 50 to 60 v.p.c. of CO_2 , the venous blood usually containing 5 to 10 v.p.c. more than the arterial.

It was first shown by Pflüger (1864) that, if whole blood were very thoroughly evacuated, all the CO_2 could be removed without the addition of acid. On the other hand, all the CO_2 in plasma could not be removed by vacuum alone. After very thorough evacuation the addition of acid or of red blood corpuscles allowed the liberation of more CO_2 . These facts suggested that, in plasma, CO_2 is present mainly as bicarbonate; for on exposure to a vacuum NaHCO_3 loses a part of its CO_2 according to the equation,



To liberate the CO_2 in Na_2CO_3 it is necessary to add acid. These results suggested, too, that the red cells contain something which can act as an acid. We now know that the hemoglobin in the red cells is an amphoteric electrolyte and hence capable of acting as an acid.

The amount of dissolved CO_2 in blood can be calculated from its solubility coefficient in blood (table 28), when the pressure of carbon dioxide with which the blood is in equilibrium is known (p. 338). The dissolved CO_2 consists in part of carbonic acid (H_2CO_3). Although the actual amount of H_2CO_3 is extremely small (being only

about 0.1 per cent of the dissolved CO_2) it is of great importance. When H_2CO_3 enters the blood, which is a slightly alkaline solution, it combines with base to form bicarbonate (BHCO_3) until an equilibrium is reached between the three forms of CO_2 :



The relative amounts of these three forms at equilibrium depend upon the pH of the solution and can be calculated from the Henderson-Hasselbalch equation:

$$\text{pH} = \text{pK}_1 + \log \frac{(\text{BHCO}_3)}{(\text{CO}_2) \text{ dissolved}^1}$$

TABLE 28
Solubility of CO_2 in physiological fluids at body temperature

FLUID	ABSORPTION COEFFICIENT ²
Water.....	0.545
Plasma.....	0.510
Red cells.....	0.44
Whole blood.....	0.48

pK_1 is a composite constant which in normal plasma has a value of about 6.1. The pH of plasma is normally about 7.4. Hence we may write:

$$7.4 = 6.1 + \log \frac{\text{Bicarbonate } \text{CO}_2}{\text{Dissolved } \text{CO}_2^1}$$

or

$$\frac{\text{Bicarbonate } \text{CO}_2}{\text{Dissolved } \text{CO}_2} = \frac{20}{1}$$

If the pH of the plasma is abnormal this ratio will, of course, be different.

The interior of the red cell is more acid than the plasma. Consequently, the ratio of bicarbonate to dissolved CO_2 will be smaller. Furthermore,

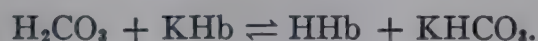
¹ At a given temperature (H_2CO_3) is a constant fraction of the dissolved CO_2 and hence does not require separate representation in the formula.

² Cubic centimeters CO_2 (measured at S.T.P.) dissolved in 1 cc. fluid at a pressure of CO_2 of 760 mm. Hg.

since the water content of the red cell is less than that of plasma, the amount of dissolved CO_2 will be less too. For these two reasons then, at the same tension of CO_2 the cells contain *less* total carbon dioxide than the plasma. Yet, as we shall soon see, the red cells play the dominant rôle in the transport of carbon dioxide.

THE RÔLE OF HEMOGLOBIN IN CARBON DIOXIDE TRANSPORT

When carbon dioxide enters the blood from the tissues it combines with water to form H_2CO_3 . This reaction is relatively slow in most solutions with a pH close to neutrality. In the blood, however, the reaction is catalyzed by an enzyme, carbonic anhydrase, which is found in the red cell but not in the plasma. The H_2CO_3 is thus formed within the cells. Nearly all of the H_2CO_3 thus formed then combines with base to form bicarbonate. The base available for combination is that which is already combined with weaker acids, mainly proteins, which are displaced by carbonic acid according to the equation,



Hemoglobin is used as the example in this equation because it does, in fact, furnish directly and indirectly, the greater part of the base used. It does so for a number of reasons. In the first place, it comprises about three-quarters of the total protein in blood. Secondly, it holds in combination an even greater proportion of the base held by weak acids in the blood, because it has so many weak acid groups in its molecule. Thirdly, it has the remarkable property of changing its acid strength with its degree of oxygenation. When the blood is in the tissues it loses its oxygen and the hemoglobin becomes a weaker acid and able to yield more base to carbonic acid. In the lungs the hemoglobin is oxygenated and becomes a stronger acid. This assists in displacing carbonic acid from combination with base and in turning it out of the blood. Figure 151 shows the titration curves of oxyhemoglobin and hemoglobin. It will be seen that at the same pH oxyhemoglobin is combined with more base than is hemoglobin, i.e., oxyhemoglobin is the stronger acid.

That hemoglobin behaved in this peculiar way was first suggested by Christiansen, Douglas and Haldane (1914), who investigated the *carbon dioxide dissociation curve* of reduced and oxygenated whole blood. As in the construction of an

oxygen dissociation curve, samples of oxygenated or reduced whole blood are brought into equilibrium in a series of saturating vessels, called tonometers, with different pressures of CO_2 . The CO_2 contents of the equilibrated bloods are then determined by analysis and plotted against the corresponding gas tensions. Christiansen, Douglas and Haldane found that the curve for oxygenated blood was lower than that for reduced blood. In other words, reduced blood could carry more CO_2 at the same tension of CO_2 than oxygenated blood (fig. 152). For many years it was

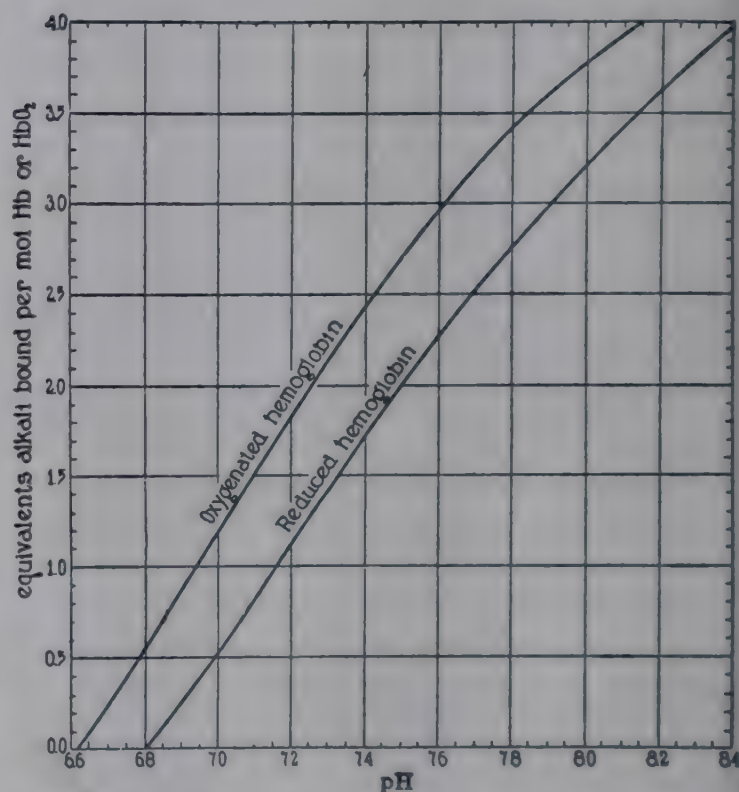


FIG. 151. Curves to show the amounts of base (K) bound by oxygenated and reduced hemoglobin at varying pH. The slopes of the curves represent the buffer values, in terms of the equivalent of base required to cause unit pH increase (from Peters and Van Slyke, *Quantitative Clinical Chemistry*, Vol. 1, 1932, from data of Hastings, Van Slyke, Neill, Heidelberger and Harington).

thought that this phenomenon was due entirely to the change in acid strength of hemoglobin on oxygenation. Reduced hemoglobin, being a weaker acid, would yield more base to carbonic acid and hence, at equal pressures of CO_2 , more bicarbonate would be formed. It now appears, however, that fifty per cent or more of this greater CO_2 -combining power of reduced blood is due to the greater power of reduced hemoglobin to combine directly with CO_2 (see p. 340).

Leaving aside the question of how the greater CO_2 -combining power of reduced blood is effected, let us consider the physiological importance of the phenomenon. By examining figure 152, it will be seen that if the blood, represented by point A

on the curve, took up 5 v.p.c. of CO_2 , from the tissues and no reduction of the hemoglobin occurred, the tension of CO_2 in the blood would rise by about 14 mm. Hg. If, however, about 6 v.p.c. of O_2 are lost from the capillary blood (as indicated by point V) the extra CO_2 can be taken

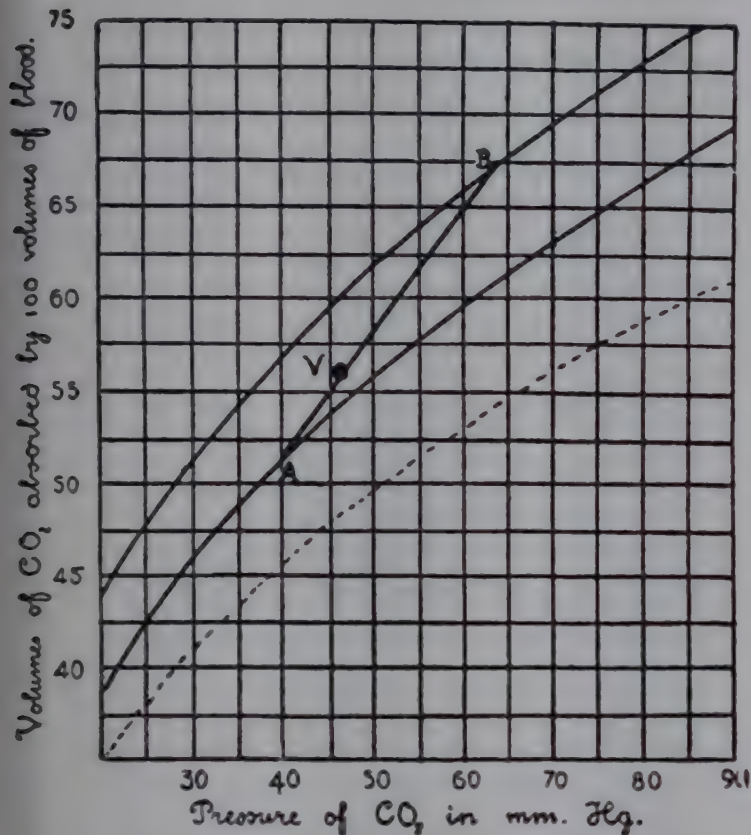


FIG. 152. Carbon dioxide dissociation curves of fully reduced human blood (upper solid line) in presence of hydrogen, and fully oxygenated human blood (lower solid line), in presence of air. Volumes of CO_2 along the ordinates; CO_2 tension along the abscissae. Line AVB is the so-called physiological dissociation curve of CO_2 , i.e., as a result of the reduction of hemoglobin the relation of volumes of CO_2 to CO_2 tension is indicated at points along this line and not along the lower curve for oxygenated blood. At A (arterial point) are indicated the volume and tension of CO_2 in arterial blood. Point B indicates the conditions in fully reduced blood. Point V (venous point) represents the degree of reduction of hemoglobin which normally occurs in the body during the passage of the blood through the systemic capillaries. The position of the line AVB varies with the respiratory quotient, moving to the right or left, respectively, with a rise or fall in the R.Q. Its position in the figure corresponds to a respiratory quotient of about 0.8. The interrupted line below is the CO_2 dissociation curve for oxygenated dog's blood. (Modified from Christiansen, Douglas and Haldane.)

on with a rise of only 7 mm. Hg in the CO_2 tension. As the change in CO_2 tension is minimized, so too is the change in the pH of the plasma, because at the lower pressure of CO_2 less free carbonic acid is present. In the lungs the reverse reactions occur. Here oxygenation of the hemoglobin reduces the CO_2 -combining power of the blood, and a smaller fall in CO_2 pressure is effective in removing the excess CO_2 .

The dominant rôle of the red cells in CO_2 transport can be further demonstrated by contrasting the CO_2 dissociation curves of *separated* plasma and *true* plasma. The latter is constructed by exposing whole blood to different pressures of CO_2 , and then separating the plasma and analyzing it for CO_2 ; the former by equilibrating plasma in the absence of red cells (fig. 153).

It is apparent that the curve for *separated* plasma is much flatter than that of *true* plasma which signifies that much larger changes in CO_2 pressure and pH accompany a given change in CO_2 content in *separated* plasma. Evidently separated plasma is not as well buffered as true plasma.

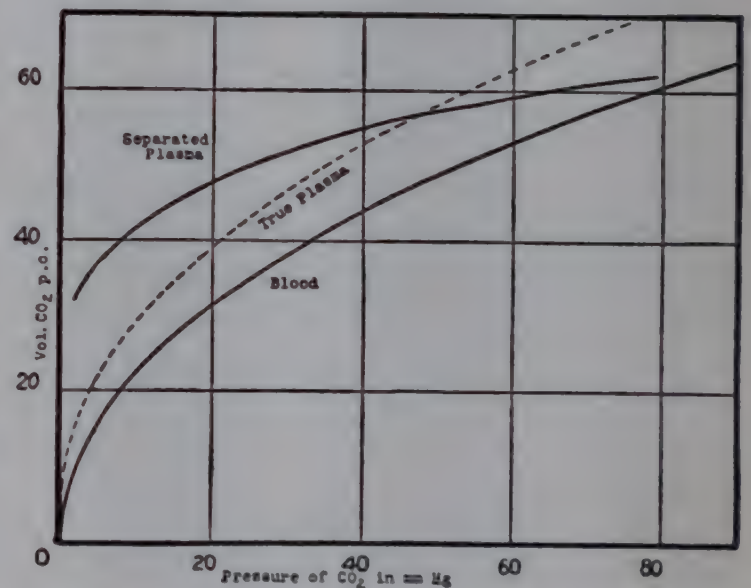


FIG. 153. Comparison between the CO_2 dissociation curves of blood and of separated and true plasma from the same blood. (After Evans, redrawn from data by Joffe and Poulton.)

The greater buffer power of true plasma must be due to the red cells. We know, however, that base ions, e.g., K^+ and Na^+ cannot pass from the red cell into the plasma, because the red cell membrane is impermeable to cations with the exception of H^+ . Consequently, the red cells must increase the buffer power of the plasma indirectly. They do so by means of the *chloride shift* or *Hamberger phenomenon*.

If CO_2 is added to whole blood and the corpuscles and plasma are analyzed separately, it will be found that:

- (1) The bicarbonate content of both plasma and corpuscles has increased.
- (2) The chloride content of the corpuscles has increased.
- (3) The chloride content of the plasma has decreased.
- (4) The metallic cation content of the corpuscles and plasma has not changed.

(5) The water content and volume of the corpuscles has increased.

The reverse changes occur when CO_2 is removed from blood by evacuation. Evidently, there is a transfer of the chloride from plasma to cells when CO_2 enters the blood, and the reverse process when CO_2 leaves the blood; hence the name, chloride shift. A simple qualitative explanation of this phenomenon can be given. When CO_2 enters the blood more HCO_3^- is formed in the corpuscles than in the plasma because they contain more available base for neutralizing H_2CO_3 . These excess HCO_3^- ions tend to diffuse out into the plasma, but, owing to the electrostatic attraction of the cations within the cells, can only do so if an equal number of Cl^- ions enter to take their place. Thus HCO_3^- from the cells enters the plasma in exchange for Cl^- which enters the corpuscles. This process will continue until an equilibrium is reached which has been found to agree (very nearly) with the distribution required by Donnan's theory of membrane equilibria (p. 103). This requires the following relations:³

$$\begin{aligned} \frac{[\text{H}^+]_{\text{cells}}}{[\text{Cl}^-]_{\text{cells}}} &= \frac{[\text{H}^+]_{\text{plasma}}}{[\text{Cl}^-]_{\text{plasma}}} \\ \frac{[\text{H}^+]_{\text{cells}}}{[\text{HCO}_3^-]_{\text{cells}}} &= \frac{[\text{H}^+]_{\text{plasma}}}{[\text{HCO}_3^-]_{\text{plasma}}} \end{aligned}$$

or

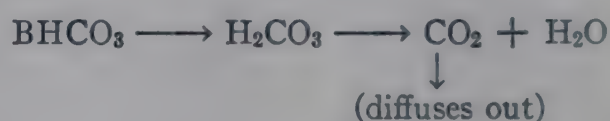
$$\frac{[\text{H}^+]_{\text{plasma}}}{[\text{H}^+]_{\text{cells}}} = \frac{[\text{Cl}^-]_{\text{cells}}}{[\text{Cl}^-]_{\text{plasma}}} = \frac{[\text{HCO}_3^-]_{\text{cells}}}{[\text{HCO}_3^-]_{\text{plasma}}}$$

The phenomenon can, in fact, be explained very precisely in terms of the Donnan theory. When CO_2 enters the blood the ratio $\frac{(\text{HCO}_3^-)_{\text{cells}}}{(\text{HCO}_3^-)_{\text{plasma}}}$ increases because more base is available in the cells. Similarly because the buffer power of plasma is less than that of the cells $\frac{(\text{H}^+)_{\text{plasma}}}{(\text{H}^+)_{\text{cells}}}$ increases. The Cl^- of the plasma must now pass into the cells in exchange for HCO_3^- until the ratios are again equalized at a new level. Since the new ratio is a higher one, the number of osmotically active particles in the cells must now be higher than in the plasma. Consequently, water enters the corpuscles to equalize the osmotic pressures of the corpuscles and plasma and the volume of the corpuscles increases. If stasis of blood occurs during the withdrawal of blood from

a vein, an abnormal amount of CO_2 may accumulate and the relative volumes of corpuscles and plasma may be appreciably altered. Hence stasis is undesirable when the blood is required for purposes where the relative volumes of corpuscles and plasma must be measured, e.g., in the estimation of blood volume.

THE EVOLUTION OF CARBON DIOXIDE IN THE LUNGS

The pressure of CO_2 in the alveoli is kept by respiratory activity at a lower level than it is in venous blood; hence CO_2 diffuses from the blood into the alveoli. This disturbs the equilibrium between the three forms of CO_2 and causes reactions to proceed in the direction indicated below:



It has been known for a long time that the reaction $\text{H}_2\text{CO}_3 \rightleftharpoons \text{CO}_2 + \text{H}_2\text{O}$ is inherently a slow one. It is known too that the blood spends only about one second in the capillaries of the lung and about the same time in the capillaries of active tissues. The velocity constants of these reactions in solutions other than blood are known too, and it can be calculated that if blood had not certain peculiar properties, the time which it spends in the lungs would scarcely allow the escape of 10 per cent of the CO_2 which we know does escape. Rapid loading and unloading of CO_2 by the blood is accomplished in two ways. The first, which has been mentioned already, is the action of the enzyme, carbonic anhydrase, which accelerates enormously, in either direction, the reversible reaction $\text{H}_2\text{CO}_3 \rightleftharpoons \text{CO}_2 + \text{H}_2\text{O}$. As carbonic anhydrase is found only in the red cells and not in the plasma, we may deduce that the rapid changes in CO_2 content occur primarily in the red cells while the plasma comes more slowly into equilibrium with the cells, perhaps after the blood has left the capillaries. Carbonic anhydrase is found in a few other locations besides red blood corpuscles. It is found in the pancreas where it may play some part in the secretion of pancreatic juice which is rich in bicarbonate. It is found also in small quantities in sperm and in muscle where its function is obscure.

The other mechanism for the rapid combination and dissociation of CO_2 in blood is the direct combination of CO_2 with hemoglobin. This reaction does not go through the stage of carbonic acid and is very rapid. For many years past the existence

³ In applying the Donnan equilibrium to the red cell the only cation which can be regarded as diffusible through the red cell membrane is the H^+ ion.

of such a compound has been generally denied. Recent experiments, however, make it appear that about twenty-five per cent of the CO_2 liberated in the lungs under normal resting conditions has been carried in the blood in direct combination with hemoglobin. Nevertheless, the total amount of CO_2 in the blood combined in this way is small; probably it never amounts to more than from 8 to 10 per cent of the total CO_2 . But the fact that reduced hemoglobin combines with more CO_2 than does oxyhemoglobin gives the compound an enhanced importance in the transport of CO_2 ;

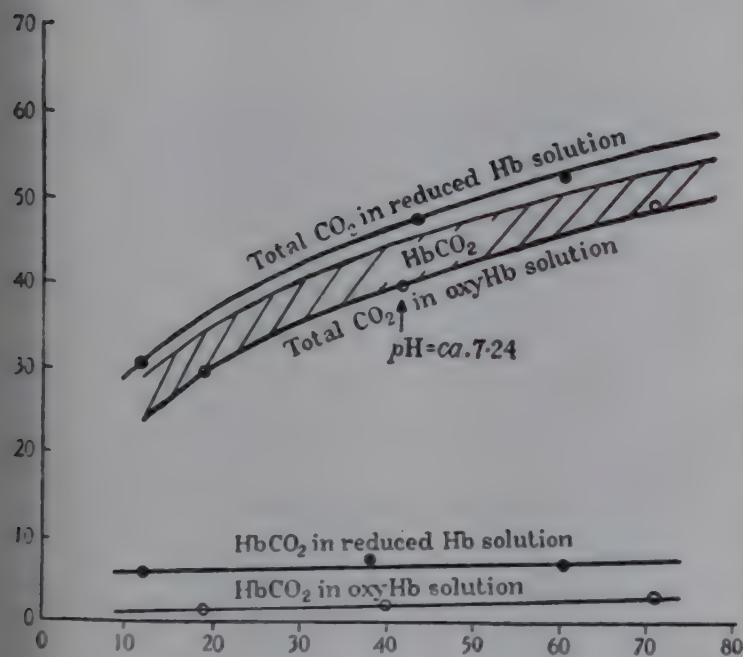


FIG. 154. Upper curves, showing the proportions of the difference in CO_2 capacity of reduced and of oxyhemoglobin which is due to the higher carbamino content of reduced hemoglobin. The shaded area represents the proportion due to carbamino CO_2 . Lower curves, showing the negligible effect of a rise in CO_2 tension upon the carbhemoglobin content of blood. (After Ferguson and Roughton, modified.)

it accounts for from 20 to 25 per cent of the gas freed in the lungs.

Carbon dioxide does not combine with the hemoglobin molecule in the same way that O_2 and CO do. It apparently combines with an NH_2 group to form a so-called carbamino-acid. Hence, one name suggested for this compound is hemoglobino-carbamic acid (Hb-NHCOOH). Another name less descriptive but possessing the virtue of brevity is carbhemoglobin.

Carbamino-compounds of CO_2 with amino-acids are well known and the technic of estimating these simpler compounds has been adapted for determining carbhemoglobin. Other forms of combined CO_2 , such as NaHCO_3 , can be precipitated as BaCO_3 by the addition of alkaline BaCl_2 . The barium salts of the carbamino-acids are soluble and remain in the supernatant fluid after centrifuging. The affinity of HB

for CO_2 diminishes with pH, and with strong acidification all the CO_2 dissociates off. Consequently, the Van Slyke technic for estimating total CO_2 can be applied to the supernatant fluid to measure the carbhemoglobin.

An increase in the CO_2 pressure of the blood should, *per se*, cause the formation of a greater amount of carbhemoglobin, but since an increase in CO_2 pressure is always accompanied by an increased acidity, which lowers the affinity of Hb for CO_2 , variations in CO_2 pressure over physiological ranges have actually little effect on the carbhemoglobin content of the blood. That is to say, the dissociation curve of carbhemoglobin is practically flat over physiological ranges of CO_2 pressure. The main factor of physiological importance in displacing CO_2 from Hb is oxygenation of the Hb (fig. 154).

SUMMARY

About 5 per cent of the total CO_2 in blood is physically dissolved. Two to ten per cent, depending on the degree of oxygenation of the hemoglobin, is combined directly with hemoglobin (carbhemoglobin). The remainder is present as bicarbonate and, as such, is combined with base which has been yielded to H_2CO_3 by the weak acids of the blood; the most important of these is hemoglobin.

The CO_2 -combining power of reduced blood is greater than that of oxygenated blood, (1) because reduced hemoglobin is a weaker acid than oxyhemoglobin; and (2) because reduced hemoglobin can combine directly with more CO_2 to form carbhemoglobin that can oxygenated hemoglobin.

Base yielded by hemoglobin participates indirectly in the carriage of CO_2 by the plasma by means of the *chloride shift*. Base within the cells neutralizes the Cl^- ions which enter the red cells, thereby leaving base in the plasma free to neutralize HCO_3^- ions.

As the blood passes through the lungs it loses a small part of its total CO_2 (i.e., about 10 per cent). The elimination of CO_2 is accomplished with minimal change in pH and in CO_2 tension by the concurrent oxygenation of the blood which decreases the CO_2 -combining power of the blood in the two ways mentioned above.

The transfer of CO_2 , to and from the blood while it is in the capillaries, can be accomplished in less than one second, because (1) carbonic anhydrase catalyzes the slow reaction $\text{H}_2\text{CO}_3 \rightleftharpoons \text{CO}_2 + \text{H}_2\text{O}$ and (2) because the formation and dissociation of carbhemoglobin is inherently rapid.

CHAPTER XXXIV

THE CONTROL OF RESPIRATION; PERIODIC RESPIRATION; DYSPNEA

THE LOCATION OF THE NERVOUS CENTERS OF THE RESPIRATORY MECHANISM. SPONTANEOUS ACTIVITY OF THE RESPIRATORY CENTER

It is customary and convenient to speak of the collections of nerve cells in the brain stem which discharge impulses to the muscles of respiration as the *respiratory center*. But the use of the term should not be taken to imply that the controlling nervous elements are in any sense a compact circumscribed mass or confined to a closely restricted area. Section through the brain at any level anterior to the upper border of the pons does not alter significantly the respiratory rhythm. But sections at various levels behind this cause pronounced disturbances in respiration. After cutting through the medulla behind the tip of the calamus scriptorius all breathing ceases. The many neurons whose integration constitute what is referred to as the respiratory center lie, therefore, over a relatively extensive area between the upper border of the pons and the lower third or so of the medulla oblongata. They are scattered at different levels through the formatio reticularis of these parts of the brain stem.

The classical experiments of Markwald (1887) form the basis of our knowledge of the location of the nervous structures controlling respiration. He described powerful and prolonged tonic inspiratory movements or "cramps" which supervened after bilateral section of the vagus nerves and division of the brain stem immediately behind the posterior colliculi. He concluded that a center inhibitory to inspiration was located in the latter situation, but that the vagi had also an inhibitory action, consequently the inspiratory "cramps" appeared only after vagal influence had been abolished as well. Markwald's observations were confirmed shortly afterwards by other experimenters. The subject was taken up in recent years by Lumsden, who found that the prolonged inspiratory movements occurred only if the section passed through the pons a few millimeters behind its anterior border and occurred whether or not the vagi were divided. The inspiratory cramps or *apneuses*, as Lumsden preferred to call them, last for several seconds. He postulated their dependence upon an *apneustic* or *inspiratory*

center at the level of the striae accousticae, which was dominated normally by an inhibitory or *pneumotaxic center* situated in the upper part of the pons. The duty of the latter center was, through its inhibitory influence, to transmute the apneustic movements into the rhythmical movements characteristic of normal respiration. After section of the brain stem behind the striae accousticae the respirations consisted of a series of gasps occurring at relatively long intervals. Lumsden concluded that these represented the activity of a primitive *gasping center* situated in the lower part of the medulla from which the two higher centers had evolved. It was considered to be of little importance in higher animals.

Lumsden's results have been confirmed in the main by Stella and by Pitts, Magoun and Ranson. Stella, however, found in contradiction to Lumsden that section through the pons (i.e. separation of the pneumotaxic center) did not result in apneusis unless the vagal influence was abolished also (see fig. 155). The results of Pitts and his associates are in essential agreement with those of Stella. They found that animals decerebrated through the upper part of the pons maintained a normal type of respiration which responded in the usual way to chemical and peripheral nerve stimulation so long as the vagi were intact, but immediately developed apneustic respiration and a complete cessation of rhythmical movements when the vagi were severed. The apneustic center is therefore under a double inhibitory influence either one of which is capable of converting the apneustic type of respiratory to the rhythm of normal or nearly normal respiration. The vagal impulses influencing the apneustic center are initiated by the stretch of the lung towards the latter part of the inspiratory phase of normal breathing (see p. 345).

The apneuses, like normal respirations, are affected powerfully by the CO_2 tension of the blood being increased in depth by having the animal breathe an air mixture containing a high concentration of CO_2 and reduced in depth, or prevented from occurring, by carbon dioxide lack (see p. 350). According to Stella, the pneumotaxic center is

bilateral but its connections with the apneustic center are mainly homolateral, i.e., uncrossed.

Pitts, Magoun and Ranson describe the respiratory center in the cat, which they locate in the reticular formation of the medulla, as consisting of an inspiratory and an expiratory division. The *inspiratory center* overlies the cephalic four-fifths of the inferior olive (fig. 156).¹ It is identified with the apneustic center of Lumsden. When stimulated a maximal co-ordinated inspiration results, involving both diaphragm and thorax. If stimulated during apneuses, the magnitude of the inspiratory movement is increased; if stimulated during an interval between apneuses an apneustic

ciprocal inhibition of one center upon stimulation of the other can be demonstrated. The similarity in the effects of stimulation of the expiratory center and of the central end of the vagus, namely, inhibition of inspiration and of apneusis, has led Pitts and his colleagues to the conclusion that the vagal respiratory effects are mediated through the expiratory center. The influence of the pneumotaxic center is probably exerted in the same way. (See also Bernthal.)

The respiratory center is connected with the motor neurones of the phrenic and intercostal nerves in the cervical (C. 3, 4 and 5) and upper thoracic segments of the cord (T. 2-6) by descend-

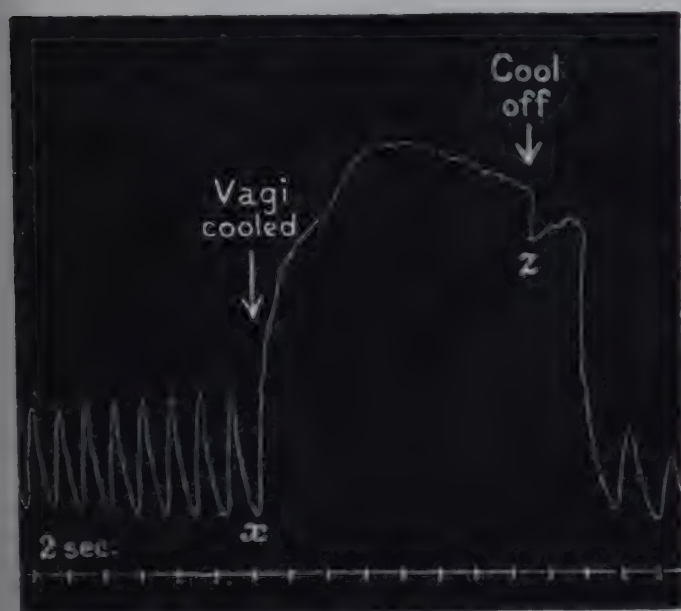


FIG. 155. Showing apneusis. Section of the brain stem along a plane passing dorsally immediately behind the posterior colliculi; and ventrally 2.5 mm. below the upper border of the pons. Between x and z the vagi were blocked by cold. Time: 2 sec. (After Stella.)

movement is produced. The *expiratory center* lies dorsal to and slightly anterior to the cephalic end of the inspiratory center. Electrical stimulation within this area causes expiration; if stimulated during inspiration or during apneusis these movements are inhibited. Regular respirations—inspiration alternating with expiration—are induced by rhythmical stimulation of the inspiratory center; expiration then occurs passively. Rhythmical stimulation of the expiratory center also produces regular respiration, spontaneous inspirations then alternating with the expiratory movements. Intimate connections exist apparently within the centers and between the two. Re-

¹ It is probable that the center is similarly located in man. Finley has described a case of respiratory failure in which a lesion was found post mortem in this situation.

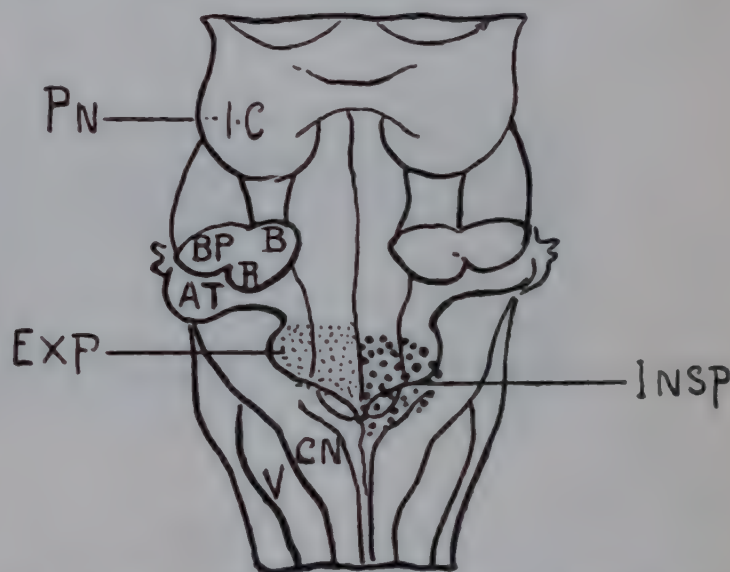


FIG. 156. Dorsal view of lower brain stem of cat showing location of pneumotaxic (Pn.), inspiratory (Insp.) and expiratory (Exp.) centers. Extent of expiratory center shown in light stippling, inspiratory center in heavy stippling. Though the centers are bilateral each is outlined on one side only, for the sake of simplicity. IC, inferior colliculus; AT, acoustic tubercle; B, brachium conjunctivum; B.P., brachium pontis; R, restiform body; CN, cuneate nucleus. (Redrawn from Pitts, Magoun and Ranson.)

ing tracts which run in the anterior columns and in the ventral part of the lateral columns of the spinal cord.

The spontaneous activity of the respiratory center has been a subject of interest to physiologists for many years. Some investigators, such as Coombs and Pike, and Schafer, have denied that the center is capable of spontaneous activity, maintaining that afferent impulses, especially those set up in the lung by the stimulus of stretch and conveyed by the vagus, and those initiated from proprioceptors in the respiratory muscles and travelling by the posterior nerve roots, were essential. However, the results secured within recent years by means of improved methods of investigation leave little reason to doubt that, in

certain species at least, the brain stem continues to discharge impulses to the respiratory muscles after all or nearly all afferent paths have been severed. For example, rhythmical bursts of impulses can be recorded from the central stump of the phrenic nerve of a decerebrate animal after section of the vagi, glossopharyngeal and other cranial nerves entering the pons and medulla, and division of the spinal cord below the level of the 7th cervical segment. Such an extensive operation would certainly interrupt all important afferent paths including those from the carotids and the aortic arch. It is not to be supposed, of course, that the respirations would be normal after such a radical procedure, for even if not essential for maintaining the activity of the center, affer-

spread through the rich interneuronal connections of the centers and enter a circus (see circus movement, p. 201), through which expiratory neurones are inhibited and inspiratory neurones excited. Thus, an apneustic inspiration is established which persists until the circus is broken, which it is after a time, as a result of reduced excitability of the neurones concerned, due in turn to the cessation of pulmonary ventilation during the apneustic period.

The grading of the strength of the contractions of the inspiratory muscles is apparently brought about by (a) alterations in frequency of the twitches of the component muscle units and (b) recruitment and derecruitment of the individual muscle units.

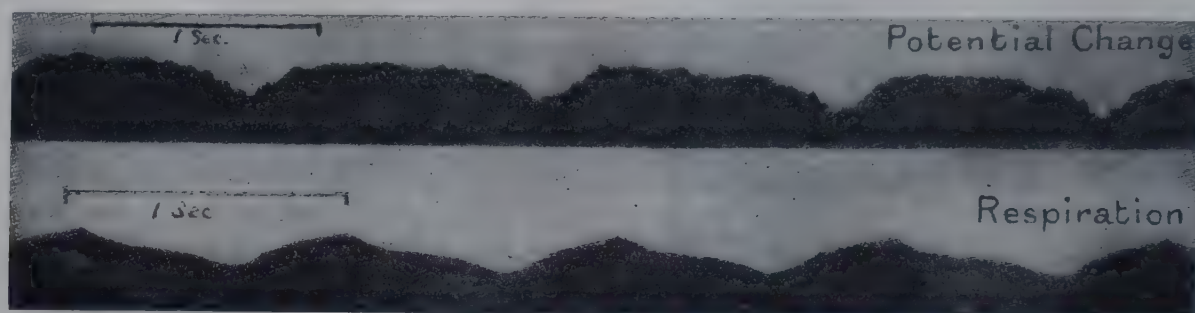


FIG. 157. Comparison of potential wave rhythm and rhythm of respiratory movements. (After Adrian and Buytendijk.)

ent nerve influences are of the utmost importance in the regulation of that activity and the production of the normal respiratory rhythm. Evidence for the automaticity of the respiratory center of a cold blooded species has been secured by Adrian and Buytenijk. They succeeded in recording rhythmical action potentials originating in the vagal lobes of the excised brain stem of the goldfish; the potential changes had the same range of frequency as the respiratory movements (fig. 157).

The spontaneous respiratory activity is apparently dependent primarily upon the inspiratory center. There is no evidence that impulses are discharged spontaneously from the pneumotaxic center. Pitts and his colleagues suggest that the pneumotaxic center is excited from the inspiratory center, that a proportion of the impulses discharged from the latter region ascend to the pontine center from whence impulses descend to the expiratory center; a discharge of inhibitory impulses is transmitted from the latter to the inspiratory center. A similar explanation is offered for the production of apneustic respiration. When the inspiratory center is cut off from the pontine and vagal influences it is postulated that impulses

Voluntary control. Emotional influences

That the respirations are under voluntary control for short periods of time is common knowledge. This control, though we are scarcely conscious of it in most instances, is being exerted in numerous ways in the ordinary affairs of daily life such as in speaking, swallowing (p. 478), laughing, blowing, coughing, sucking, etc. But the power of the will to inhibit respiration is strictly limited. The breath can be held for only a brief space (about 45 seconds) before automatic or involuntary control asserts itself; the inhibitory influence is overriden and the muscles of respiration contract despite all one's efforts to "hold the breath" (see also p. 350). The nerve elements giving origin to the voluntary impulses are probably in the motor area of the cerebral cortex. Stimulation of area 6a in monkeys accelerates the respirations; area 6b is inhibitory.

The respirations may be effected profoundly by impulses arising in higher cerebral centers as a result of various emotional or other mental states e.g., fear, grief, surprise, interest, amusement, etc.

Reflex control

Hering-Breuer reflexes. The importance of afferent impulses from the lungs in the control of respiration was first pointed out in 1868 by Hering and Breuer, who showed that inflation of the lungs arrested inspiration, expiration then ensuing, while deflation inhibited expiration and brought on inspiration. These are reflex effects, mediated through the afferent fibers of the pulmonary vagi, for they are abolished after these nerves have been divided. In ordinary breathing the inflation re-

deflation of the lungs is required, as can be produced in the laboratory by forcible compression of the chest, by collapse of the lungs through the production of a pneumothorax, or by sucking air from the trachea.

Head, in a later study of these reflexes in Hering's laboratory, isolated a slip of the diaphragm and recorded its action during distension and deflation, respectively, of the lungs. When the trachea was clamped towards the end of a normal inspiration the muscle slip immediately relaxed



FIG. 158A. Records of impulses discharged over vagus nerve during inflation of lung. Spinal cat, single fiber preparation. Inflation of the lungs by pump. Movement of signal line directly proportional to inflation. A, inflation = 65 cc., maximum frequency, 80 per second; B, inflation = 115 cc., maximum frequency, 120 per second; C, inflation = 230 cc., maximum frequency, 250 per second. (After Adrian.)

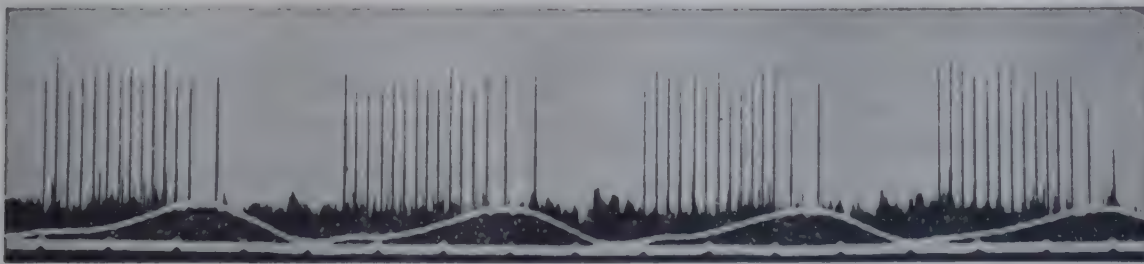


FIG. 158B. Showing discharge of impulses over a single fiber of the phrenic nerve during artificial respiration (wavy line) in a curarized animal. (After Partridge.)

flex alone comes into play, thus checking, at the end of an inspiration of the usual duration, further distension of the lungs. When the inhibitory vagal influence is abolished by cutting the nerves the respiratory rate, as might be expected, is slowed, for the inspiratory phase then continues for a longer period before it gives place to expiration. As mentioned on page 342 inspiratory movements of such length as to abolish rhythmical respiration follow if the inhibitory influence emanating from the pontine (pneumotaxic) center is excluded as well. The corresponding deflation reflex does not apparently play a part under ordinary conditions (Adrian, Partridge). In order to elicit it, extreme

and the inspiratory movement ceased. Blocking the trachea at the end of expiration called forth a powerful inspiratory movement; sucking air from the lungs caused a tonic contraction of the diaphragm.

Adrian approached the problem by recording during the phases of respiration the action potentials passing up a single afferent vagal fiber. The frequency of the impulses was found to vary with the degree of stretch of the lung, being highest when lung inflation was greatest (i.e., at the end of the inspiratory phase) and lowest when deflation was more nearly complete (i.e., towards the end of expiration) (fig. 158A). The receptors

which, as intimated above, are sensitive to a stretching force, are thought to be situated in the walls of the alveolar ducts, the most distensible parts of the lung structure. They adapt slowly (p. 806), for a stream of impulses continues to ascend the nerve with relatively little reduction in frequency while inflation of the lung is maintained.

There are many interesting points to be considered in connection with the effect of vagus nerve impulses on the rhythm of respiration, two of which may be mentioned here. (1) It was observed by Stewart, Pyke and Guthrie that the rhythm of respiration in a case which had been resuscitated from brain anemia was the same as that of the artificial respiration which was given during the resuscitation process. (2) It is easy to show, when phrenic impulses (fig. 158B) are recorded by a valve amplifier in a curarized animal, that the rhythm of the respiratory center comes into phase with that of the artificial respiration. The phrenic impulses coincide with the inspiratory phase of artificial respiration as long as the vagi are intact. This correlation is lost when the vagi are cut.

CAROTID AND AORTIC REFLEXES

Heymans and Heymans made the surprising discovery in 1927 that respiratory reflexes could be elicited from the aortic area. This discovery and the brilliant researches of Heymans and his associates, in the years following, on the corresponding role played by the structures in the region of the carotid bifurcation opened a new field in the physiology of respiration, and a fresh outlook upon the vexed question of respiratory control. Many preconceptions and misconceptions have been swept aside. A more detailed description of these areas has been given in Chapter XXVII where their functions in the control of the vascular system were discussed.

The carotid and aortic areas each contain two types of receptors; one type (pressoreceptors) responds to mechanical, the other (chemoreceptors) to chemical stimulation. The pressoreceptors situated among the collagenous fibers in the wall of the carotid sinus and in the wall of the aortic arch, are stimulated by a stretching force, as by a rise in arterial blood pressure. The chemoreceptors are contained in small gland-like structures—the *carotid* and *aortic bodies* (p. 240). The respiratory reflexes initiated from these two types of receptors are contrary in their effects.

Stimulation of the pressoreceptors inhibits respiration, an abrupt rise in blood pressure such as follows the injection of adrenaline causing respiratory arrest (apnea). Excitation of the chemoreceptors increases the rate and depth of breathing. Both types of reflex are abolished by section of the supplying nerves (sinus or aortic).

Though of the utmost importance in the control of the circulation, the *pressoreceptors* do not appear, in mammals at least, to serve any respiratory function under physiological conditions. There is no circumstance of a physiological nature under which the inhibition of respiration is caused by a rise in blood pressure or by the stimulation of these receptors in any other way. Nor is it apparent that such a reaction would serve any useful purpose. That they give a respiratory response when very strongly stimulated appears to be accidental and without physiological significance. They may possibly represent the vestige of a mechanism which was of value in some aquatic ancestral form and to which the mammalian body has fallen heir.

The *chemoreceptors* are stimulated by oxygen lack, but not, according to Schmidt and Comroe, until the oxygen tension of the arterial blood reaches a relatively low level—probably a little below 70 mm. Hg in man. At this tension the arterial blood is about 92 per cent saturated with oxygen. An anoxemia of this grade is approximately equivalent to that caused by breathing an air mixture containing 18 per cent of oxygen or by ascending to an altitude of 4000 feet (fig. 160).

The chemoreceptors are less sensitive still to carbon dioxide. When, for example, the carotid body is isolated from the general blood stream (effect upon the respiratory center thus eliminated), but its nerve supply retained, and then perfused with a solution containing CO_2 , the smallest change in CO_2 tension which causes an appreciable change in respiration is around 10 mm. Hg. When, on the other hand, the reflex effect is abolished by denervation of the carotid area, a change in CO_2 tension of only 3 mm. Hg in the blood supplying the respiratory center is sufficient to induce hyperpnea (Schmidt, Dunkley and Dripps).

Schmidt and his associates conclude from their experiments that the chemoreceptors do not play a rôle in the control of respiration under ordinary physiological conditions. This conclusion receives support from the observations of Cromer and Ivy

who found that dogs worked just as well on a treadmill after as before excision of the carotid bodies. Also, according to Dautrebande, a dog with its carotid and aortic chemoreceptors removed

and ultimate failure of the central neurons is the predominant effect of oxygen lack. The chemoreflex mechanism, on the other hand, according to Comroe and Schmidt, is highly resistant to

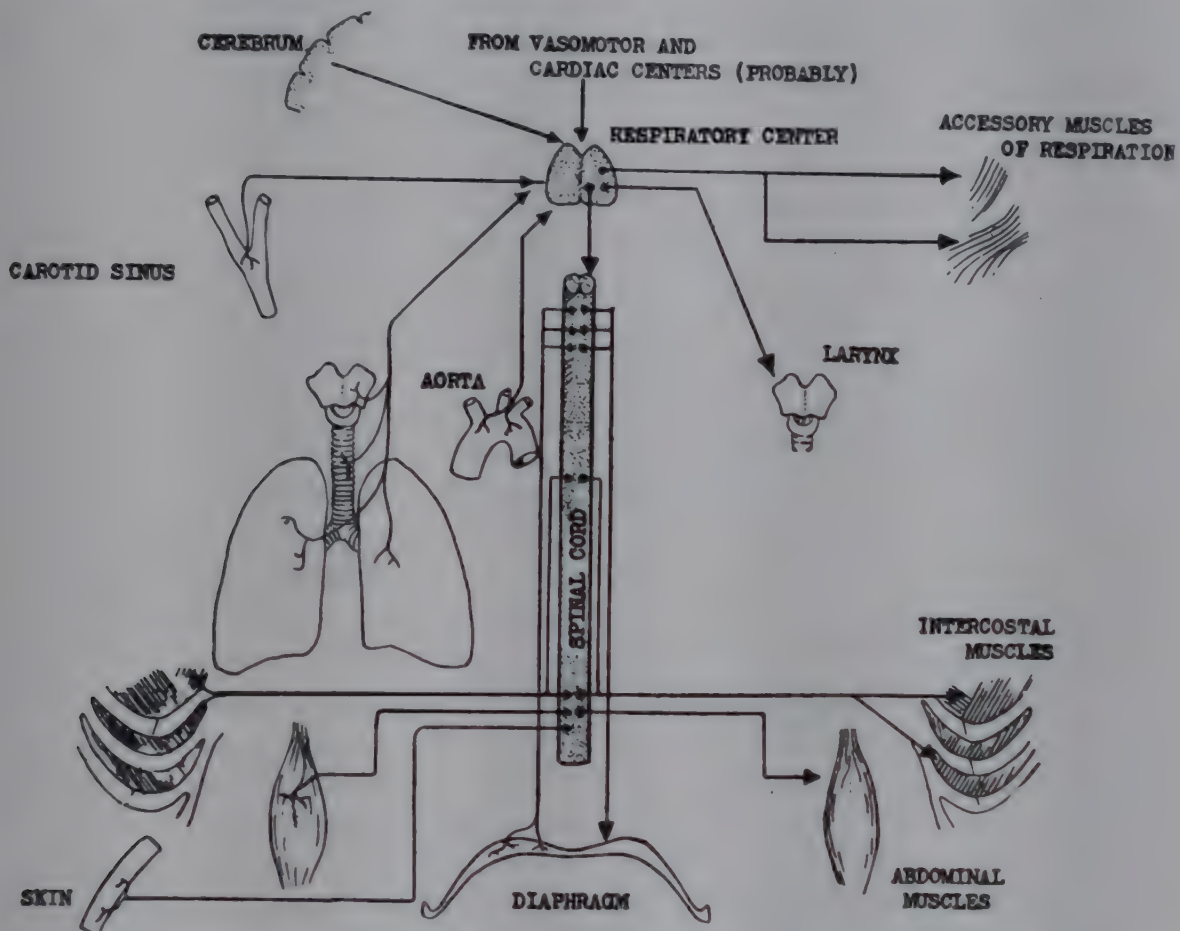


FIG. 159. Diagram to illustrate the nervous control of respiration.

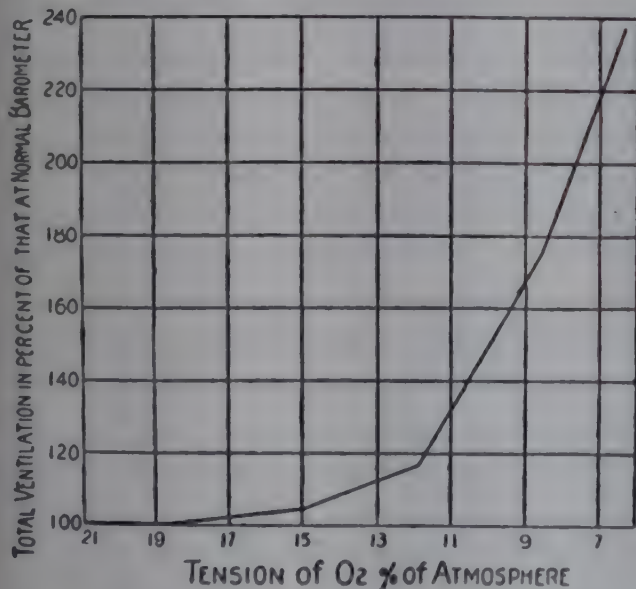


FIG. 160. Effect of oxygen lack upon pulmonary ventilation in human subject. (After Means.)

carries out respiratory adjustments to high altitudes as well as a normal animal.

In more exacting emergencies, however, the reflex response of the chemoreceptors, especially to anoxia, is undoubtedly of the highest importance. Anoxia appears to be ineffective as a stimulus to the respiratory center. Depression

anoxia, retaining its viability and continuing to exert its influence upon the center which otherwise would be unresponsive in the body's emergency. These observers look upon the chemoreceptor mechanism as a more primitive type of respiratory control which serves as a last line of defense against respiratory failure—the *ultimum moriens* of the respiratory control system.

The chemoreceptors also appear to be relatively insensitive to the H ion. Such slight variations in hydrogen ion concentration of the blood as might occur under any condition of health could have little or no stimulating effect upon them. In experimental animals a relatively large shift in pH (namely 0.1) of the fluid perfusing the isolated carotid body is required in order to effect a change in respiration.

It should be mentioned in fairness to any discussion of the importance of the chemoreceptors in the control of normal breathing, that there is not universal agreement with the views just given. Records of the action currents in the sinus nerve show that impulses are discharged by the chemoreceptors in response to much smaller changes

in gas tensions of the arterial blood than those given above. It has been reported that a reduction in oxygen tension below 85 mm. Hg causes an increase in the activity recorded from the "chemical fibers" of the sinus nerve. Even during normal breathing, action currents can be recorded from the sinus nerve from which all but a few "chemical fibers" have been severed. There are two possibilities which throw some doubt on the validity of evidence derived from such studies, namely, that the impulses may not have their source in the chemoreceptors and that they may not affect the activity of the respiratory center even though they are of chemoreceptor origin. Still, the experiments of Watt, Dumke and Comroe who used respiratory activity as the index of chemoreceptor stimulation, provide evidence for tonic chemoreflex activity. They found that the inhalation of pure oxygen by unanesthetized dogs caused a reduction in breathing of as much as 31 per cent. This indicates that before the administration of oxygen the breathing had been under tonic chemoreflex control. The authors, concluded, nevertheless, that such control was not essential for normal breathing, because in some of their animals, the respirations, after an initial reduction, were restored to their original value although pure oxygen was being breathed. Watt and his associates support their belief in the absence of any significant influence, under ordinary conditions, upon the respiratory center through chemoreceptor mechanisms by the observation that no change in breathing follows denervation of the sinus.

REFLEXES INITIATED IN OTHER PARTS OF THE BODY

Stimulation of almost any afferent nerve may bring about a reflex change in respiration. Stimulation of pain fibers is especially potent in this regard and the respiratory effects of the excitation of the cutaneous nerves by extremes of heat or cold are well known. The great increase in pulmonary ventilation occurring in muscular exercise is to a large extent dependent upon reflexes originating in the active muscles. Proprioceptive impulses from the diaphragm and other respiratory muscles during one respiratory phase exert an important influence upon the succeeding movement.³ Stimulation of the abdominal viscera,

either during surgical operations or as a result of disease, may cause profound changes in breathing. The glossopharyngeal nerve contains afferent fibers which inhibit respiration during the second stage of the act of swallowing. Abrupt inhibition of respiration is also caused by the inhalation of an irritant gas through stimulation of nasal branches of the 5th nerve. In other instances irritation of these endings may cause sneezing—a modified respiratory act (see fig. 158). Coughing, though it can be brought about by a voluntary effort, is most commonly reflex in character, initiated by the stimulation of afferent nerve endings in the trachea and larynx (p. 303).

Important as is the rôle of CO₂ in stimulating respiration, even very high concentrations (9 per cent and higher) of the gas in the inspired air are not capable of inducing the greatest pulmonary ventilation possible. During strenuous muscular work the volume of air breathed by a vigorous man may amount to 120 liters per minute, whereas about 60 liters per minute is the maximum ventilation caused by the inhalation of high concentrations of CO₂. Yet in the latter instance the sense of effort (dyspnea) is, as pointed out by Barcroft and Margaria, much greater. The greater pulmonary ventilation caused by muscular exercise as compared with that resulting from the inhalation of CO₂ is due, it appears, to reflexes originating in the contracting muscles and possibly also to the irradiation of impulses from the motor cortex to the respiratory center (p. 348). Comroe and Schmidt have demonstrated the occurrence of pronounced hyperpnea (in both men and animals) upon passively exercising the limbs, which was abolished or very much reduced by section of the nerves but not by obstructing the circulation to the exercised limb.

The action of sensory impulses on the respiratory center is conditioned (1) by the afferent nervous impulses arriving at the center from other regions and (2) by the chemical environment of its cells. To illustrate (1) stimulation of the saphenous nerve in a dog causes acceleration of respiration with perhaps little change in amplitude. If the vagi are cut and the saphenous again stimulated there may be little effect on the rate but perhaps a definite change in amplitude (Gesell).

experiments suggest that a chemoreflex mechanism is present in this situation, but his results have so far not been confirmed by other workers. As Gesell has pointed out, the existence of such a chemoreceptor organ would explain the rapid breathing caused by multiple pulmonary emboli (p. 346) and by pulmonary edema.

³ Larsell has described specialized sensory endings in the lung tissue which possibly are chemoreceptor in function. The lung tissue would be an even more advantageous site for sampling the oxygen content of the blood than is the carotid or aortic arch. Pi Suner's

(2), inhibitory (vagal) and accelerator (saphenous) respiratory reflexes are reduced by a high CO_2 tension. During the period of low CO_2 tension of the blood following the injection of sodium carbonate (see below) stimulation of the saphenous nerve produces a greater increase in the respiratory rate than if the carbonate had not been injected (Gesell). Conversely, stimulation of the central ends of the vagus and saphenous nerves during the hyperpnea due to CO_2 excess causes less effect than does similar stimulation of these nerves during normal breathing.

CHEMICAL STIMULATION OF THE RESPIRATORY CENTER

The chemical control of respiration under ordinary physiological conditions is carried out through the action of carbon dioxide on the respiratory center. Haldane and Priestley found that in man a rise in the carbon dioxide of the alveolar air of only 0.2 per cent (equivalent to an increase of 1.5 mm. Hg pressure) was sufficient to *double* the pulmonary ventilation. It has already been pointed out (p. 346) that the chemoreceptors of the carotid and aortic bodies are relatively insensitive to the action of CO_2 .

Though there has been some difference of opinion on the subject, and some conflict between the experimental results of different investigators, it seems fairly well established that the effect of anoxia upon the center is mainly if not entirely one of depression rather than of excitation.

The manner in which carbon dioxide serves as a stimulus to the center has also been a subject of debate for a number of years. According to the view at one time, the activity of the center was regulated by the hydrogen ion concentration of the arterial blood, carbon dioxide serving as a stimulus simply because, in solution, it acted as an acid (H_2CO_3). Several facts, however, could not be reconciled with this idea. For example, sodium carbonate and sodium bicarbonate when injected into the blood stream in amounts which caused equal increases in blood pH had opposite effects upon respiration, the former salt reducing and the latter increasing pulmonary ventilation. Furthermore, carbon dioxide produced a much greater effect on respiration than did any other acid for a given pH change. The work of Jacobs threw light upon these apparently discrepant observations. He showed that, owing to the more ready penetration of carbon dioxide into cells, the intracellular H-ion concentration might be considerably higher than that of the surrounding fluid medium. When the petals of a certain blue flower (*Symphytum perigrinum*) which are pink

in an acid medium and blue in an alkaline one, were immersed in a solution of sodium bicarbonate (pH 7.4), they turned pink. Gessel, taking these observations into account, formulated a theory of respiratory control which dispelled much of the confusion surrounding the theory of the H-ion being the essential respiratory stimulus. He postulated that the determining factor was the hydrogen ion concentration *within the cells of the center itself*. The opposite effects of sodium carbonate and sodium bicarbonate upon the respirations were explained on the view, supported by experiment, that the carbonate lowers the CO_2 tension of the blood and thus leads to a greater flow of CO_2 from the tissues, whereas the carbon dioxide tension of the blood and tissues is increased by the bicarbonate. This conception seemed to establish the hydrogen ion concentration of the nerve cells as the paramount common factor in the chemical stimulation of the respiratory center, whether this was due to CO_2 , fixed acids, anoxia or reduced blood supply to the center. The latter two conditions, it was pointed out, would permit the accumulation of acid metabolites (which ordinarily are removed by oxidative processes) within the nervous tissue. Thus the center, stimulated by the acid products of its own metabolism, increased the pulmonary ventilation, in order, as it were, to satisfy its own oxygen requirements and so the needs of the body as a whole. It should be remembered, however, that at this time the chemoreceptors of the carotid and aortic bodies and their respiratory function were unknown. It appears now that the observed effects of anoxia upon respiration were due not to a direct action upon the center, but to reflexes initiated from these structures (p. 346). Nor is the hyperpnea caused by fixed acids due apparently to their direct effect upon the center, for the latter is less sensitive to a rise in H-ion concentration due to such acids than are the chemoreceptors. The hyperpnea of diabetic and other types of acidosis is probably of chemoreceptor origin.

To return to the question, "How does CO_2 act as a stimulus to the respiratory center?" Does it do so merely by raising the hydrogen ion concentration of the cells of the respiratory center, its greater power of penetrating cell boundaries rendering it more effective in this regard? There is reason to believe that CO_2 acts specifically upon the center, that is, in some way other than by raising the H-ion concentration. Krogh and his associates found, for example, that in human sub-

jects, though the hyperpnea caused by the inhalation of CO_2 was extreme, little change in arterial pH resulted. The ingestion of ammonium chloride, on the contrary, while producing a much more pronounced lowering of the pH of the arterial blood caused little or no increase in breathing. It would seem that the question of the greater penetrating power of carbon dioxide can be ignored in considering these results, for the experiments in which ammonium chloride was ingested were continued over a period more than long enough (up to 10 days) for the cells of the center to have come into equilibrium with the arterial blood. Bernthal points out, however, that though equilibrium may have become established between the concentrations of hydrogen ions in the arterial blood and in the respiratory center, there is reason to believe that there may not have been *equality* of concentrations and that, therefore, the arterial blood might not be a true indicator of the concentration of hydrogen ions within the cells. This problem of the action of carbon dioxide—whether due to some specific property as well as to its effect in raising the hydrogen ion concentration or to the latter effect alone has not been finally solved. It must be admitted that if it acts specifically, the manner in which it does so is unknown.

Any condition apparently which profoundly alters the relationship between their oxygen supply and the metabolic need at the time serves to stimulate the chemoreceptors. The immediate stimuli, it is thought, are the acid products of their own metabolism. Thus, not only anoxia but poisoning the cells with cyanide or sulphide, ischemia of the carotid body, or increasing its metabolism as by the application of heat, are all capable of eliciting a hyperpneic reflex. When, on the other hand, glycolysis is prevented by local poisoning with monoiodoacetic acid, which prevents the production of lactic acid, anoxia does not cause the usual respiratory response. The chemoreceptors, then, are seen as highly specialized cells capable, as it were, of sampling the blood for its oxygen content and, when necessary, of signalling a message to the respiratory center when the tissues generally are threatened with a dangerous degree of anoxia.

HYPERPNEA, FORCED BREATHING AND APNEA

Hyperpnea. An increase in the quantity of air breathed (minute volume) as a result of an in-

crease of either the rate or depth of respiration or of both, is called hyperpnea. Hyperpnea may be produced by impulses reaching the respiratory center from the cerebral cortex (as in excitement and other emotional states) or from the hypothalamus; by the stimulation of sensory nerves (e.g., pain, heat or cold applied to the skin, etc.), by conditions which increase the demand of the tissues for oxygen, e.g., muscular exercise, and by certain other factors to be mentioned in the section under dyspnea.

Apnea. If the lungs of an animal are over-ventilated for a minute or two, either by stimulating a sensory nerve and thus inducing reflex hyperpnea or by means of some mechanical respiratory device, a period follows during which all breathing is suspended. This period of respiratory arrest is called *apnea*. Apnea can also be induced by sending a stream of inhibitory impulses to the respiratory center, as by stimulating the central end of the vagus nerve or by distending the lungs and maintaining them in the inspiratory position, e.g., by clamping the trachea towards the end of inspiration. An apneic period can also be induced by the stimulation of the pressoreceptors in carotid sinus as may result from a sharp rise in blood pressure (p. 346) or by a direct chemical action upon the respiratory center, e.g., the injection of sodium carbonate into the blood stream or by the action of certain depressant drugs.

Any person can readily induce apnea in himself by overbreathing. When one breathes deeply and quickly for a few minutes and then stops he does not have any desire to breathe for the next minute or more. The deep and rapid breathing is termed *voluntary hyperpnea* or *forced respiration*.

The apnea following overventilation is due to the excessive elimination of carbon dioxide and in consequence to the lowering of the tension of this gas in the blood. Forced breathing in an atmosphere rich in carbon dioxide therefore does not cause apnea. Owing to the shape of the oxygen dissociation curve of hemoglobin, oxygenation of the arterial blood can be only slightly improved by forced breathing, and is therefore of little significance in the production of the apnea. Indeed, in the apneic periods of Cheyne-Stokes respiration there may actually be oxygen want sufficient in degree to cause pronounced cyanosis (Haldane and Poulton). Nevertheless, when forced breathing is carried out in an atmosphere rich in oxygen apnea may continue, in some instances, for as

long as 15 minutes (Schneider); the high percentage of oxygen in the inspired air causes a slight increase in the oxygen tension of the blood and in the tissues (Argyll Campbell).

Other effects of forced breathing

While the cardinal features of the reaction to forced breathing are now well known, there is considerable variety in detail when observed over a large number of cases. Variations seem due not alone to differences in rate and degree of the overventilation but to peculiarities which, for lack of a better understanding of them, may be termed constitutional and temperamental. In a class of over a hundred students two or three individuals may be found who can carry on forced breathing for ten minutes with comparatively little disturbance. On the whole these seem to be of rather robust physique, though not necessarily trained athletes.

Probably the first subjective observations of the student will be dizziness and faintness resulting in some relaxation of his efforts, but it is very rarely that a feeling of nausea becomes prominent.³ This initial discomfort may arise from a disturbance of the circulation directly due to the too vigorous movements of the chest, and for this reason instructions are given to assume the supine position and to force the depth rather than the rate of breathing. Within five minutes at the most, a regular rhythm has been established and the subject will have begun to notice numbness and tingling, probably coolness and perhaps tremors in various parts of the body and slight tightening of the muscles. In the majority of cases, samples of alveolar air taken at this time will show a level of carbon dioxide about one-half the normal, and only a slight further drop will occur as the experiment continues. The pulse and blood pressure will have risen, as would be expected with muscular exercise, but from now on signs and symptoms will begin to vary. The pulse and blood pressure may retain their relationship, or the pulse may rise without corresponding rise in pressure, but not infrequently the pulse rate increases while the pressure falls. It is usually in this last group of cases that one may find the cold clammy skin, pale cyanosis and thready pulse which form a curious anomaly. If enough hemoglobin is reduced to cause cyanosis it obviously is not holding its oxygen by reason of the alkalosis, and therefore the circulation must in some manner be restricted. The loss of carbon dioxide may interfere with the efficiency of the heart. There is evidence of vasoconstriction of the peripheral vessels, and vasodilatation of the vessels in the splanchnic area has been observed during surgical operations. Good evidence of circulatory disturbance exists in the coldness of the extremities. The condition is suggestive

of shock, and students who have experienced it may be impressed with the contrast to the flushed warm skin and pounding heart which occur when the breath is held to the breaking point (see also pp. 213 and 250).

Tetany varies from a slight stiffness of the muscles to well-marked contractures. In the hand the most common attitude is ulnar flexion with relative extension on the radial side and some flexion of the wrists. Before it is clearly evident it may occasionally be brought out by constricting the upper arm (Trousseau's sign). It would be expected on this account that tetany in the hands would appear first on the side upon which the blood pressure cuff has been applied, but in practice, this seldom occurs and occasionally even the reverse is true, suggesting that the interference with venous return incident to the blood pressure readings tends to delay the phenomenon. Tetany in the face can often be detected at a distance by a peculiar appearance of the eyes associated with a contraction of the surrounding muscles, particularly the inner part of the under lid. The involvement of deeper muscles can be brought out in the alterations of speech; occasionally the orbicular muscles of the mouth are considerably affected. A few subjects will note particularly contractions in the abdominal muscles and in the legs.

The hyperexcitability of the nervous system is almost always shown in the increased briskness of the knee jerk, but particularly in the facial nerve reflex elicited by tapping just below the zygoma (Chvostek's sign). On the whole this has proved one of the best early signs of the altered acid-base balance. The response can easily be distinguished from the reaction of an unexpected stimulus and from the vibration due to continuity of tissue. It makes its appearance as fine but definite contractions occurring around the eye, nose or corner of the mouth. Whereas in the knee jerk some comparison is made with the previous normal response, this is unnecessary in Chvostek's sign, so that the latter should be of more value in clinical examinations. Sometimes clonic spasms and shivering will persist through the greater part of an experiment.

It is after the first five minutes that certain temperamental differences may also appear. Whereas many, perhaps more cautious, keep themselves well in hand, coöperate easily in the taking of the samples and can stop the moment the signal is given, there are others, perhaps more adventurous, who develop symptoms more quickly, have a little difficulty in giving samples and finally have trouble in coming to a halt. Of the latter group some become somnolent and a few will appear amused and if set laughing have difficulty in controlling themselves. The condition has been described as one of mild intoxication, and in classes immediately after the war a student who had been an aviator remarked that his sensations resembled those resulting from a very rapid rise in altitude (see p. 361). The inability to stop promptly may be due in part to some

³ These observations on voluntary hyperpnea were kindly placed at our disposal by our colleague, Dr. Edward Fidler.

dulling of the special senses which is not appreciated by the student until during the apneic period he notes that sounds become closer and clearer. But this does not seem to be the sole reason of the difficulty, because occasionally, having been brought to a stop for a few seconds, the subject will break back into the previous rhythm. This condition suggests a loss of control of the upper over the lower neuron, a marked contrast to the state of affairs at the beginning of the experiment. It also resembles a fixation of ideas. If cyanosis be present, the inference can be made that the stagnant type of anoxia (p. 359) can occur with forced breathing—an apparent paradox.

The apneic period is variable in length depending on the degree of disturbance and is, of course, prolonged if oxygen is taken during the last few breaths of the forced breathing. Whether cyanosis has appeared before or not it is almost certain to be present with an apnea of more than thirty seconds. During long periods the change may be very striking where the texture and color of the skin enhance the contrast.

the famous London surgeon of the 18th century.) In this type of breathing the respirations may be described as alternately waxing and waning. That is, a period of breathing occurs in which the individual respirations are small and slow to start with but gradually increase in depth and rate to a maximum and then, subsiding again, finally cease for a time (fig. 161). The hyperpneic and apneic phases last each for about 30 seconds. Periodic breathing of this type occurs at high altitudes and is exhibited by such animals as the ground hog and the dormouse during hibernation. A tendency to this type of breathing is not uncommonly shown by healthy infants and occasionally by normal adults during sleep. The most common clinical conditions in which Cheyne-Stokes breathing occurs are advanced renal and cardiac disease, asthma and raised intracranial pressure. It is also seen in severe pneumonia and in morphine

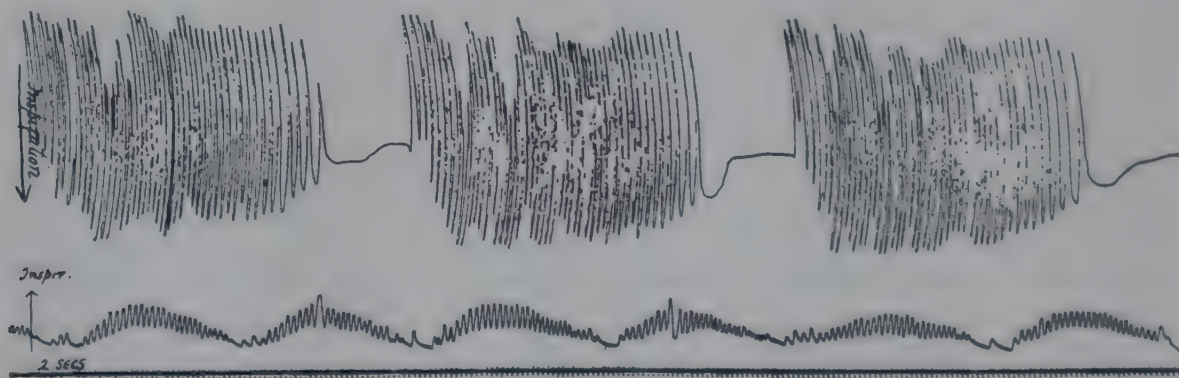


FIG. 161. Two examples of Cheyne-Stokes breathing. (After Lewis.)

The return of breathing occurs more frequently with a single breath, usually rather small, followed by a secondary apnea. Succeeding movements gain in extent while apneic periods decline until normal breathing is reached. Typical Cheyne-Stokes breathing, which at one time was considered a common characteristic, has been quite rare. In several hundred experiments carried on by students during the past fifteen years only one striking case has appeared in which the phenomenon continued over a space of four or five minutes.

The decrease in acidity of the urine has been demonstrable in most of the tests but disappointing results occasionally occur where the acidity is low before the experiment and the forced breathing is of mild character.

PERIODIC RESPIRATION

Periodic breathing is the term applied to various types of uneven respiratory rhythm. The most common type is called Cheyne-Stokes breathing after two physicians who described it. (It had been described earlier, however, by John Hunter,

and chloral poisoning, or it may follow a general anesthetic. As mentioned above, it occurs, though rarely, after a bout of forced breathing. Douglas and Haldane induced it in normal persons by a moderate degree of oxygen want. Clinical Cheyne-Stokes respiration is usually a grave omen and is probably the result, in most instances at any rate, of damage to the respiratory center caused by oxygen lack. The latter may be the result of defective aeration of the blood in the lungs or of slowing of the circulation through the medulla (e.g., circulatory failure or raised intracranial pressure). The periodic rhythm is abolished in many cases by oxygen administration. It is apparently developed in the following way. The depressed state of the respiratory center results in weak shallow respirations which intensify the anoxia. The oxygen lack stimulates the respirations and, according to Douglas and Haldane, also increases the sensitivity of the center to CO_2 . The respirations increase in vigor but subside as the CO_2 is eliminated. The period of

breathing, however, has reduced the CO_2 tension of the blood below the level at which the center is stimulated; apnea ensues. The apneic period, of course, increases the anoxia and prevents the elimination of CO_2 ; the center is stimulated directly, as well as through a chemoreceptor reflex and the breathing returns, but ceases again when, through the absorption of oxygen and the blowing off of CO_2 , the center is no longer excited. It has also been pointed out by Douglas and Haldane that the elimination of large quantities of CO_2 from the body during the hyperpneic periods and the ultimate reduction of the bicarbonate reserve removes a steadying influence which is normally exerted upon the respiratory center. (They compare this effect to that of the fly-wheel of a motor.) The body normally holds a large store of CO_2 in the lungs and tissue fluids (as bicarbonate) which is drawn upon to oppose any sudden fall in CO_2 tension of the blood supplying the respiratory center. Any sharp increase in CO_2 tension, on the other hand, is prevented through the excess CO_2 being buffered by the tissue fluids. In Cheyne-Stokes breathing the reduction of the bicarbonate reserves permits slight changes in the gas tensions to produce sudden and exaggerated fluctuations in the activity of the center. CO_2 administration as shown by Allen and Pembry abolishes in many instances the periodic rhythm.

A manner in which periodic breathing might possibly be produced in cases of raised intracranial pressure is suggested by an experiment of Eyster. He increased the intracranial pressure in dogs and found that when the arterial blood pressure rose and fell alternately above and below the intracranial pressure, Cheyne-Stokes breathing ensued. In clinical cases of raised intracranial pressure similar alternating elevations and depressions of the blood pressure have been observed by Eyster, the hyperpneic phase coinciding with the blood pressure rise. The blood pressure changes may be the immediate cause of the respiratory rhythm in these cases. It is easy to conceive that a fall in arterial pressure below intracranial pressure by causing acute anemia of the center would suppress its activity for the time and induce apnea; this would give place to hyperpnea during the phase of raised arterial pressure when blood again filled the vessels of the center.

A type of respiratory periodicity known as Biot's breathing is seen in disease, e.g., meningitis, involving the region of the medulla. This differs from the Cheyne-Stokes type in that the onsets of the apneic and hyperpneic phases are abrupt. The two phases are frequently also unequally spaced.

DYSPNEA

Definition

Dyspnea means literally difficult breathing. When the respirations from whatever cause cannot be carried out with ease and practically unconsciously the individual is said to be dyspneic. The term therefore generally implies a subjective element. Dyspnea thus differs from hyperpnea. The latter term means simply increased pulmonary ventilation, and this may occur quite unconsciously or if the subject is aware of the augmentation of the breathing there is not necessarily any sensation of difficulty or distress. When the hyperpnea becomes extreme and yet leaves the need for which it had been instituted unsatisfied, discomfort or distress is experienced and the term dyspnea is applicable. Meakins offers the following concise definition; "dyspnea is the consciousness of the necessity for increased respiratory effort."

THE CAUSES OF DYSPNEA

Since the respiratory and circulatory functions are directed toward the acquisition of oxygen and the elimination of carbon dioxide, dyspnea may result if either of these functions be disturbed to such an extent that the normal gaseous exchanges cannot be accomplished. On the other hand the oxygen requirement and the carbon dioxide production may be so great that the *normal* respiratory and circulatory mechanisms find difficulty in meeting the demands of the moment. Or again the supply of oxygen itself may be inadequate as a result of a low oxygen tension in the atmosphere (e.g., high altitudes). In considering the causes of dyspnea we must therefore in many instances look beyond the lungs themselves. The lungs are the bellows but it is of course the tissues which consume oxygen and produce carbon dioxide; and it is the heart and the blood which are concerned with the carriage of these gases between lungs and tissues. As already mentioned dyspnea is the sensation of respiratory distress. The height of the hyperpnea at which dyspnea appears is called the *dyspneic point*. There is a relationship between the latter and the *vital capacity*. A person with a large vital capacity obviously can breathe a larger volume of air without discomfort than can one with a smaller vital capacity. There is a closer relationship however between the onset of dyspnea and the ratio of the *functional residual air* (that is, the quantity of air in the lungs at the end of

an ordinary expiration) to the *total lung capacity*, (i.e. the total volume of air which the lungs can hold during full inspiration (p. 308)). In health the ratio is about 2 to 5. The more nearly equal are the volumes of the functional residual air and the total lung capacity, the greater will be the tendency to dyspnea.

The fundamental or immediate causes of dyspnea can in most instances be reduced to the following categories. (1) Stimulation of the respiratory center either (a) reflexly from the carotid and aortic bodies (anoxia or increase in H-ion concentration due to fixed acids), (b) directly, by CO₂ excess, (c) a combination of (a) and (b) as in asphyxial states, or (d) by impulses from cerebral centers or by afferent impulses, especially of a painful character, from abdominal or peripheral regions. (2) Hypersensitivity of the Hering-Breuer reflex, thus bringing about earlier inhibition of the inspiratory phase and causing as a consequence a more rapid shallow type of breathing.

The chief abnormal conditions associated with dyspnea are:

(1) Prevention of adequate oxygenation of the blood in the lungs. That is, anoxia of the anoxic type (p. 358). This may result from (a) pulmonary disease or from laryngeal or tracheal obstruction, or (b) low O₂ tension in the inspired air, e.g., high altitudes.

(2) Interference with the transport of the respiratory gases (a) circulatory failure, (b) anemia—anoxia of the stagnant and anemic types respectively.

(3) Restriction of the action of the diaphragm or intercostals.

(4) *Acidosis*, reduced alkali reserve or retention of CO₂ (gaseous acidosis).

(5) Increased metabolism.

(6) *Nervous conditions*, e.g., emotional disturbance, neurasthenia, hysteria, encephalitis, or the direct stimulation of the respiratory center by cerebral tumor, hemorrhage or edema.

Dyspnea due to pulmonary diseases

Dyspnea is a feature of various respiratory diseases.

(a) In some instances, e.g., laryngeal or bronchial obstruction and asthma, the dyspnea is due to a combination of anoxia and CO₂ retention.

(b) In other instances owing to the reduced distensibility of the lungs resulting from edema, congestion, inflammation, fibrosis, etc., the Hering-Breuer reflex is abnormally sensitive.

(c) Limitation of the movements of the diaphragm and chest wall. In emphysema, for example, owing to the loss of lung elasticity the resting position of the chest is one of nearly full inspiration. The diaphragm is fixed and the thorax elevated. Any further enlargement of the chest entails unusual effort on the part of the intercostal muscles (see also p. 368) and the enlistment of the accessory muscles of respiration. Expiration involves active contraction of the expiratory muscles.

Cardiac dyspnea

Dyspnea upon exertion is a feature of certain chronic heart lesions, e.g., mitral stenosis. Stimulation of the carotid and aortic bodies by oxygen want or of the respiratory center by carbon dioxide excess is not *in the absence of cardiac failure*, responsible for the dyspnea, since the oxygen saturation of the arterial blood is not reduced to any important degree and the carbon dioxide tension is within or even below the normal range. Pulmonary engorgement leading to diminished distensibility of the lung is considered by Meakins, Christie and associates to be the prime cause of cardiac dyspnea. Though the reduction in the vital capacity may be roughly proportional to the dyspnea, the two do not bear the relationship of cause and effect, since the subject's vital capacity is always greater than the volume of air required for the exertion which causes the dyspnea. Owing, however, to the diminished distensibility—the stiffness of the lung—a greater inspiratory effort is expended in breathing the extra volume of air which the muscular exertion demands. The lung might be compared to stiffened bellows leather; more force is required to distend it. The elasticity of the lung is also moderately reduced so that expiration instead of being a passive act brought about largely by the recoil of the lung now requires the aid of the contraction of expiratory muscles in order to “squeeze” the air from the chest. The intrapleural pressure, therefore, instead of remaining “negative” throughout the respiratory cycle becomes positive toward the end of expiration (Christie and Meakins). The decreased distensibility of the lung, for the same reason that it increases the difficulty of enlarging the volume of tidal air, reduces the vital capacity. In other words the dyspnea and reduced vital capacity are due to a common cause. The reduced distensibility will also have the effect as already mentioned, of increasing the sensitivity

of the Hering-Breuer reflex with the production of shallow breathing.⁴

In *congestive heart failure* with marked slowing of the circulation there is commonly hyperpnea and dyspnea even during rest and then there may be added to the pulmonary factor itself the stimulating effect of carbon dioxide excess upon the respiratory center but, according to Christie and Meakins, this is of minor importance. When pulmonary edema supervenes, interference with the absorption of oxygen and the production of arterial anoxemia (stimulation of carotid body) may possibly be a factor. Hindrance to the absorption of oxygen, caused by the presence of exudate in the alveoli and the edematous swelling of the alveolar walls, is accompanied by little or no interference with the elimination of carbon dioxide; this is probably due in part to the much greater solubility of carbon dioxide than of oxygen and, in consequence, to the freer diffusion of the former gas through the edema fluid. Nevertheless, in congestive heart failure arterial anoxemia with a normal or even a subnormal carbon dioxide content of the arterial blood may exist even in the absence of pulmonary edema. Unequal ventilation of the alveoli—underventilation of some and over-ventilation of others—is probably the principal cause of the anoxia (chapter XXXV) in these instances (p. 365). Diminished distensibility and elasticity of the lung would tend to favor the ventilation of peripheral alveoli at the expense of those placed more centrally. In other words, the normal tendency towards unequal ventilation of the alveoli is exaggerated by diminished distensibility of the lung tissue.

Experimental support can be cited for the view that reduced distensibility of the lungs as a result of congestion is an important factor in cardiac dyspnea. Harrison and his associates have shown that increased pressure in the pulmonary capillaries causes rapid, shallow breathing which is abolished by vagal section. The production of multiple emboli in the pulmonary capillaries by the intravenous injection of starch granules causes congestion of the lungs and rapid shallow breathing (p. 366) and Partridge has shown that after rapid breathing has been induced in this way the impulses recorded from the vagus nerve are of higher frequency than those resulting from inflation to an equal degree of normal lung. It has also been shown that in man pulmonary conges-

tion does actually reduce the distensibility of the lung tissue.

Harrison and his colleagues found in subjects of cardiac failure the CO_2 content of the jugular blood to be within normal limits and observed no significant reduction in the cerebral blood flow (i.e., through the respiratory center). They suggest that afferent impulses initiated from the great veins at the base of the heart as a result of the high venous pressure, as well as impulses from the congested lungs, excite the respiratory center.

Though there is much to be said for the reflex origin of cardiac dyspnea, not all are agreed as to its paramount importance. McMichael, for example, in a clinical study found a reduction in cardiac output in those subjects showing hyperpnea (which is always associated with the dyspnea) during rest. The hyperpnea showed a closer correlation with the cardiac output than with the vital capacity which, he points out, is contrary to what might be expected were congestion of the lungs the dominant causative factor. He is inclined to believe that the hyperpnea and dyspnea of the cardiac patient *during rest* is due to reduced blood flow through the center (i.e., chemical stimulation).

ORTHOPNEA. In congestive heart failure with dyspnea at rest the breathlessness is usually more pronounced in the recumbent than in the sitting position. When propped up with pillows the patient may be quite comfortable but becomes dyspneic when he lies down. Many theories have been advanced in attempts to explain the less difficult breathing in the upright position. Among these are:

(a) Removal of the weight of the abdominal viscera which interferes with the descent of the diaphragm in the recumbent position.

(b) Better draining of blood from the medulla and in consequence, augmentation of the flow through the respiratory center.

(c) Draining of blood from the chest and the relief of pulmonary congestion. This is probably the most important factor. The distensibility of the lung is thereby increased and the Hering-Breuer reflex rendered less sensitive. The vital capacity is less in the recumbent than in the sitting posture. This is true even for the normal person but in cardiac cases the effect is accentuated by the vascular engorgement and decreased distensibility of the lung induced by recumbency. Nevertheless, as already mentioned, reduction in the vital capacity is not itself responsible for the dyspnea.

⁴ The beneficial effects of morphine upon cardiac dyspnea are very probably brought about through the reduction in the sensitivity of the vagal endings.

CARDIAC ASTHMA. This is the term applied to paroxysmal attacks of dyspnea occurring, usually at night, in subjects of heart disease associated with hypertension and advanced arteriosclerosis. The upright position tends to relieve the dyspnea. The cause of the attack is unknown, though Christie and Meakins suggest that it is due to pulmonary congestion and a sudden decrease in pulmonary distensibility. During the attack, according to Weiss and Robb, there is engorgement of the pulmonary vascular bed, a tendency to pulmonary edema and a marked reduction in the oxygen saturation of the arterial blood.

Dyspnea in anemia

When at rest, the anemic subject is as a rule not dyspneic. The hemoglobin though reduced in amount becomes fully saturated with oxygen in the lungs. The oxygen tension and consequently the quantity of the gas in simple solution in the arterial blood are normal. The arterial blood of a patient whose hemoglobin is 30 per cent of the normal value will, however, contain only a little over 6 volumes per cent of oxygen. In the healthy resting body the blood in its passage through the capillaries gives up at least 5 volumes per cent. If the velocity of blood flow through the tissues in anemia were the same as during health a unit volume of blood would give up an equivalent amount of oxygen. This would leave a reserve of only 1 volume per cent, i.e., the venous blood would be almost completely reduced. The great proportion of the oxygen load of the blood would be supplied to the tissues at a very low pressure (see dissociation curve, p. 320) and anoxemia would result. The circulation rate (cardiac output) is, however, increased in anemia so that each unit of blood gives up a smaller part of its oxygen load. The oxygen is therefore delivered to the tissues at a higher pressure than would otherwise be possible. For this reason the patient is not dyspneic while resting even though his hemoglobin is greatly reduced.⁵ Not only is the output of the heart increased but a redistribution of the blood occurs. The vessels of the skin are constricted and a greater proportion of the total blood volume is driven through other regions. The extent to which the circulatory readjustments can compensate for the blood defect is limited, therefore during exertion the extra demand for oxygen cannot be met.

⁵ Fahr and Ronzone reported a case in which the hemoglobin was 12 per cent of the normal and the arterial blood contained only 2.2 volumes per cent of oxygen. There was no dyspnea during rest.

Oxygen want follows, the respiratory mechanism (carotid body) is stimulated; hyperpnea and dyspnea result.

It is to be remembered that in anemia the carriage of carbon dioxide may also be interfered with since hemoglobin constitutes an essential part of the mechanism provided for the transport of this gas (see chapter XXXIII).

Dyspnea due to increased metabolism

IN HEALTH, muscular exercise is the outstanding cause of a great increase of metabolism. Carbon dioxide is produced in excessive amounts both from oxidative processes and by the interaction of lactic acid with bicarbonate and acts as a powerful stimulus to the respiratory center. The increased pulmonary ventilation in exercise is due in part only to stimulation of the center by CO_2 . Reflexes initiated in the active muscles and the irradiation of impulses from the motor cortex also play an important part (p. 349). As the severity of the exercise is increased, hyperpnea merges into dyspnea. The athlete and the untrained person differ widely in respect to the degree of muscular exertion which will produce this physiological type of dyspnea. The difference depends upon the following factors:

(a) *Vital capacity.* In the average normal man the pulmonary ventilation increases from 4 to 5 fold before the dyspneic point is reached. The athlete on the other hand, since his vital capacity is greater shows a correspondingly greater increase in his pulmonary ventilation before dyspnea supervenes. The existence of any pulmonary condition which reduces the vital capacity will depress the level of the dyspneic point.

(b) *Circulation rate.* The trained man can increase his circulation rate to a greater degree than the untrained and so deliver more oxygen to his tissues at high pressure.

(c) *Neuromuscular integration.* Co-ordination of the several muscles in a given muscular act is more precise in the trained than in the untrained man. There is thus less waste of effort. In the performance of a given amount of work, therefore, the untrained man consumes a greater volume of oxygen, i.e., he is a less efficient machine. Yet his respiratory center appears to be more sensitive to nervous influences—impulses from the contracting muscles and from the cerebral cortex.

A PATHOLOGICAL INCREASE IN METABOLISM, e.g., hyperthyroidism, fever, etc., cannot apparently in the absence of some respiratory or circulatory abnormality cause dyspnea during rest. The increase in metabolism would need to be

around 300 per cent before dyspnea might be expected to occur and such a metabolic level is never reached in these or any other pathological condition. Nevertheless, in hyperthyroidism dyspnea will follow upon a degree of exertion which would cause no distress in a healthy person, for the greater metabolic rate, due to the disease, added to that of the exercise will increase the metabolism sufficiently to raise the pulmonary ventilation above the dyspneic point. The dyspnea of hyperthyroidism, when pulmonary and cardiovascular complications are absent is therefore like that of anemia, evident only upon exertion. In hyperthyroidism there is also a reduced vital capacity (which will lower the dyspneic point) as well as a diminution of muscular efficiency.

Dyspnea due to acidosis

The importance of the part played by pulmonary ventilation in resisting a rise in the hydrogen ion concentration of the body fluids has been dealt with elsewhere (p. 107). Little more need be said here. Non-volatile acids, e.g., lactic in muscular exercise, β -hydroxybutyric and acetoacetic acids in diabetes, and retained acids in nephritis, react with bicarbonate. The alkali reserve becomes reduced, but the ratio,

$$\frac{\text{H}_2\text{CO}_3}{\text{NaHCO}_3} = \frac{1}{20}$$

is maintained through the stimulating effect of CO_2 upon the respiratory center. It is thus that the CO_2 tension of the alveolar air (and so of the

arterial blood) is kept at a level proportional to the reduction in the denominator of the equation. When this can no longer be effected, i.e., when the hydrogen ion concentration of the blood rises, the acidosis being then uncompensated, the center is stimulated mainly through reflexes initiated from chemoreceptors of the carotid and aortic bodies.

J. B. S. Haldane produced a severe acidosis and dyspnea in himself by the ingestion of acid forming salts (CaCl_2 and NH_4Cl). But as a matter of fact, the production of fixed acids in diseased conditions rarely causes such a high degree of hyperpnea that dyspnea results, unless the circulatory and respiratory mechanisms are very inefficient or the metabolic rate is increased. According to Means the "alkali reserve" must drop to around 12 volumes per cent before dyspnea supervenes as a result of the acidosis itself. In milder grades of acidosis, however, dyspnea, as in hyperthyroidism occurs upon exertion. The hyperpnea due to the increased metabolism of the exercise is then added to that due to the acidosis, with the result that the dyspneic point is soon reached.

Carbon dioxide retention may, as in emphysema, be accompanied by a compensatory rise in bicarbonate and a normal blood reaction (compensated CO_2 excess); dyspnea is not a notable feature in this condition. In other instances of CO_2 retention compensation is incomplete (uncompensated CO_2 excess or gaseous acidosis) and dyspnea results. In others, again, the CO_2 retention is due to the depression of the respiratory center itself, as in morphine narcosis; in such instances, though compensation is incomplete, dyspnea of course does not occur.

CHAPTER XXXV

ANOXIA

CLASSIFICATION AND DEFINITIONS

The failure of the tissues, for any reason, to receive an adequate supply of oxygen is called *anoxia*, *hypoxia*, *oxygen lack* or *oxygen want*. Anoxia may result from (a) defective oxygenation of the blood in the lungs, (b) lowered oxygen capacity of the blood, or (c) slowing of the movement of blood through the capillaries. Upon the basis of these three causes, oxygen want has been classified by Barcroft into *anoxic*, *anemic* and *stagnant* types, respectively. A fourth type, the *histotoxic* (Gk. *histos*, tissue, and *toxikon*, poison), caused by poisoning of the oxidative processes of the tissues has been added by Peters and Van Slyke. *Anoxemia* is a term which denotes a low tension of oxygen in the arterial blood, and is used synonymously with anoxic anoxia. *Asphyxia* is sometimes used interchangeably with anoxia, but, strictly speaking, this term should be restricted to conditions in which there is anoxia combined with an increased tension of carbon dioxide in the blood and tissues.

THE ANOXIC TYPE OF ANOXIA [HYPOXIA]

Normally, as we have seen, the blood leaves the lungs only about 95 per cent saturated with oxygen. When it reaches the tissues it contains, therefore, about 19 volumes per cent of oxygen when normal oxygen capacity is 20 vols. per cent. Oxygen is consequently at high pressure in the plasma. During rest only 5 volumes or so per cent of the gas are abstracted, i.e., the mixed venous blood coming to the lungs contains about 14 volumes per cent (around 70 per cent saturated). As will be seen from the dissociation curve of oxyhemoglobin the supply of this quantity of oxygen is associated with a drop in oxygen pressure to only 40 mm. Hg or so. A high pressure gradient from capillary to tissue cells is therefore assured. In the anoxic type of anoxia the saturation of the arterial blood and the oxygen partial pressure are reduced. When the saturation is, say, 50 per cent, there are still 10 volumes per cent of oxygen in the blood available for the tissues. Since the latter require only 5 volumes, 10 volumes apparently should be adequate. But this load is held at a relatively low pressure, about 25 mm. Hg. In order then for the blood in the capillaries to supply the necessary 5 volumes per cent, i.e., in order for the oxy-

gen saturation to be reduced to only 25 per cent, the pressure must fall to around 15 mm. Hg. The oxygen obviously must be delivered at a very low pressure head even were the pressure at zero within the tissue cells. It has already been pointed out that the intracellular pressure is considerably above zero and that, in the case of muscle at least, a lowering of the oxygen tension in the blood, the blood-flow remaining constant, cuts down the oxygen consumption of the tissues.

The chief clinical manifestations of the anoxic type are; dyspnea (p. 353), cyanosis (p. 372), mental disturbances, e.g., exhilaration, delirium, mania or fixed ideas. The intensity of the effects upon the body of a low oxygen tension in the arterial blood is influenced by (a) the abruptness of the onset of the anoxemia, (b) its degree, (c) its duration and (d) the general physical condition of the body.

The anoxic type of anoxia is produced by the following conditions:

- (1) Low oxygen tension in the inspired air:
 - (a) Vitiating of the atmosphere by inert gases.
 - (b) High altitudes, mountain sickness.
- (2) Abnormalities of the pulmonary mechanisms, pneumonia, asthma, emphysema, collapse of the lung, pulmonary edema or water in the lungs of the nearly drowned, obstruction of the air passages and paralysis of respiration.
- (3) Direct communication between the right and left sides of the heart through which venous blood is short circuited—shunt.

THE ANEMIC TYPE

The anemic type is caused by (a) *hemorrhage* or *anemia* from whatever cause, (b) *carbon monoxide poisoning* (p. 372), (c) *poisoning by nitrites and chlorates* which like carbon monoxide form stable compounds with hemoglobin (p. 46). In the anemic form of anoxia (resulting from anemia) (a) the total load of oxygen is reduced in proportion to the reduction in the hemoglobin. The oxygen tension and consequently the amount of the gas in simple solution is, however, the same as in health and the hemoglobin present in the arterial blood is 95 per cent saturated. In other words what hemoglobin there is, holds its full oxygen

load. Yet a great fall in oxygen pressure must occur in the capillary blood in order that the tissues shall receive their quota of oxygen, for, since there are fewer red cells each must give up a larger part of its load than normally. As a consequence, therefore, unless the rate of blood flow increases a large part of the oxygen supply must be delivered at low pressure (see also p. 356).

THE STAGNANT TYPE

In the anoxia due to a slowed circulation, the saturation of the arterial blood, its total oxygen load and its oxygen tension are all normal. A large part of the oxygen supply is, however,

blood flow, the blood of an arm vein having the oxygen saturation of arterial blood.

THE HISTOTOXIC TYPE

In this type, as its name implies, the respiratory mechanisms of the tissues are poisoned. The cells are unable to use the oxygen carried to them and, as a result, the capillary and venous bloods contain more oxygen and has a higher oxygen tension than normally (see Cyanide poisoning, p. 372).

The four types of anoxia are represented in figure 162. It will be noted that in the anoxic type only, is the arterial saturation low. In the

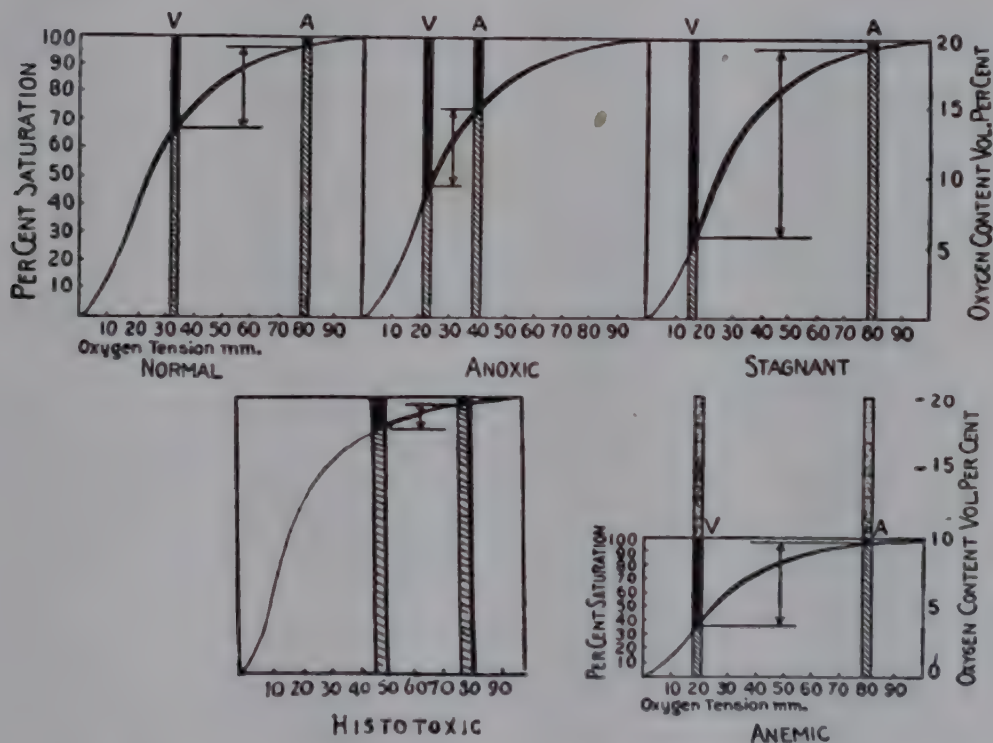


FIG. 162. Diagram illustrating types of anoxia. Columns representing arterial blood (A) and venous blood (V) are superimposed upon the oxygen dissociation curve. The black portion of the column represents reduced hemoglobin and the shaded portion, oxygenated hemoglobin. In the case of anemic anoxia the dotted portion of the columns represents hemoglobin that is either lost, as in true anemia, or unfit for oxygen transport, as in carbon monoxide poisoning. The perpendicular arrows denote the volume of oxygen given up to the tissues from a unit of blood. (After Means, with additions.)

delivered under low pressure, since each portion of blood gives up a larger proportion of its load owing to the slower blood flow, and its longer stay in the capillaries. Slowing of the circulation from whatever cause will induce the stagnant type of anoxia. It therefore occurs in the following conditions: (a) *heart failure*, (b) *obstruction of the venous return from a part (local anoxia)*, and (c) *surgical shock*. Pronounced slowing of the peripheral blood flow can be readily induced in a normal person by the application of cold. Meakins and Davies found that the venous blood of an arm vein was completely reduced after the hands had been kept in cold water for a time. Hot water, on the other hand, speeded up the peripheral

first two types the saturation of the hemoglobin in the venous blood is subnormal. In the anemic type, the hemoglobin, although reduced in amount, is nearly fully saturated, as in health. In the histotoxic type, as a result of the action of the poison upon the oxidative processes of the tissues (p. 372) the oxygen saturation of the venous blood approaches that of arterial blood.

CONDITIONS ASSOCIATED WITH THE ANOXIC TYPE OF ANOXIA

LOW OXYGEN TENSION OF THE INSPIRED AIR

Vitiation of the Atmosphere by Inert Gases

The atmosphere may have a low oxygen tension yet the barometric pressure be no lower than

usual. That is, other gases are present which displace the oxygen and so reduce its percentage in the atmosphere. In mines for example the air may contain "Fire Damp" (methane) or "Black Damp" (nitrogen, CO_2) which lower the percentage of oxygen in the air though the barometric pressure is actually higher than that at sea level. These gases, under such circumstances produce no direct deleterious effect upon the body. They act simply by reducing the oxygen tension of the atmosphere. They therefore differ in this respect from carbon monoxide (p. 371), which when occurring in mines in dangerous concentrations is spoken of as "after damp."

Mountain sickness

At high altitudes the percentage of oxygen in the atmosphere is the same as at sea-level but the barometric pressure is low and the partial pressure of oxygen is reduced to a corresponding degree. If the barometer, for example, registers a pressure of 600 mm. Hg the oxygen pressure is $\left(\frac{20.96}{100} \times 600 =\right)$ 125.76 mm. Hg. Mountain sickness as first shown by Paul Bert is due to the low partial pressure of oxygen in the atmosphere and to the resulting anoxemia, not to the low barometric pressure itself. The effects resulting from breathing atmospheres low in oxygen but possessing a high total pressure are in many respects similar to those of mountain sickness. On the other hand if an animal be placed in a steel chamber and the barometric pressure lowered to $\frac{1}{4}$ or $\frac{1}{2}$ of an atmosphere no ill effects result, provided the air is enriched with oxygen, i.e., if its percentage be raised to maintain its partial pressure at the normal figure.

The first signs and symptoms of oxygen want usually make their appearance in healthy unacclimatized persons when they ascend to an altitude of 10,000 feet or more above sea-level. The height at which mountain sickness appears varies considerably, however, in different individuals depending upon their fitness, the rapidity with which the ascent is made and upon the degree of muscular effort undertaken. From 23,000 to 25,000 feet is around the limit to which unacclimatized men can ascend without the aid of an artificial oxygen supply. Though in the attempt to scale Mount Everest's peak in 1924 a height of

around 29,000 feet was reached. The two of the party of this expedition, George Mallory and Andrew Irving, who ascended to the greatest height lost their lives. Their bodies were not recovered and it is not known whether they died as a result of oxygen want, exposure or by falling. In 1875 the three French scientists, Crocé-Spinelli, Simon and Tissandier ascended in a balloon. A height of over 26,000 feet (Bar. 270 mm. Hg) was reached. Consciousness was lost at about 25,000 feet. When Tissandier regained consciousness the balloon was falling rapidly, but his two companions were dead. Oxygen containers were carried in the ascent but Tissandier records that his arms became powerless and so he was unable to raise the mouthpiece to his lips. In 1901 Berson and Simon made a balloon ascent with the aid of oxygen to 36,000 feet. In recent years aeroplane and balloon ascents to much higher altitudes have been made (72,395 feet by Stevens and Anderson in 1935). Aeroplane ascents above 12,000-13,000 feet without oxygen are risky.

Several mountain climbing expeditions have been made in the past by different groups of physiologists for the purpose of studying the effects of low oxygen tensions upon the respiratory functions and of determining the factors underlying the phenomenon of acclimatization. An expedition was made to Mont Rosa (15,000 feet) in 1894 by Mosso and by others subsequently; to the peak of Teneriffe (12,000 feet) in 1910 by Zuntz, Barcroft and associates, and in 1912 to Pike's Peak (14,100 feet) by the Anglo-American expedition of which Haldane, Douglas, Henderson and Schneider were members. In 1921-1922 Barcroft headed a party to Cerro de Pasco (14,200 feet) in the Peruvian Andes. A Himalayan expedition was led by Hartman in 1931, and in 1935 Dill led a party to the Chilean Andes.

It may be useful to the reader to remind him of certain fundamental physical principles involved in ascents to high altitudes before considering the physiological effects. As the pressure becomes reduced with increasing altitude the gases of the atmosphere and in the lungs must, of course, expand. It follows that the quantity of oxygen and other gases of the atmosphere per unit volume becomes reduced proportionately. For this reason at great altitudes (above 28,000 feet) the inhalation from a cylinder of even pure oxygen will not

prevent anoxia.¹ The pressure of oxygen in the lungs of a person breathing pure oxygen at a height of say 40,000 feet would be only about 60 mm. Hg and his arterial blood only 88 per cent saturated with oxygen. A closed cabin containing air at a higher pressure (equivalent to an altitude of around 8,000 feet) is the only way in which the problem of anoxia in high altitude flying can be solved satisfactorily. Even then there is the danger of leaks, especially in military flying from enemy action. Were the airmen thus suddenly exposed to the low pressure existing at altitudes above 35,000 feet, acute anoxia would result, consciousness being lost within a few seconds.

GENERAL SIGNS AND SYMPTOMS. Aeroplane ascents, if made rapidly without the use of oxygen, may result in sudden loss of consciousness due to the reduction in oxygen supply to the brain. When the ascent is made more slowly, or the altitude is not so great as to cause immediate loss of consciousness, the aviator may at first experience sensations of excitement, exhilaration and well-being. As higher altitudes are reached effects of a more serious nature develop, often insidiously. Mental and sensory dullness, muscular weakness, headache, vomiting, cyanosis, dyspnea and perhaps a tendency toward periodic breathing may be induced. A common and dangerous effect is the development of fixed ideas which may result in the performance of foolhardy and ill-judged actions.

When a person climbs to a mountain height the time taken in the journey allows a certain degree of physiological readjustment to take place and the symptoms are usually less intense. But, in the case of the aviator, mental features, e.g., feeling of elation, exhilaration, talkativeness and sometimes emotional outbursts, laughing or crying, quarrelsomeness or the development of fixed ideas, are prominent. Mental tasks, e.g., calculations, memory tests, and telling the time from

A rough calculation will make this clear. At 40,000 feet the atmospheric pressure is about 141 mm. Hg, i.e., less than $\frac{1}{3}$ the pressure at sea level. A unit volume of air, therefore, contains less than $\frac{1}{3}$ as much oxygen as the same volume at 760 mm. Hg pressure. A given volume of pure oxygen would contain less than the number of oxygen molecules at 40,000 feet as would at sea level. That is to say, a given space at former level could not contain as much oxygen as a corresponding volume of air would contain at the pressure of 1 atmosphere. Making allowance for the pressure of water vapor (47 mm.) and CO₂ (36 mm.) the partial pressure of oxygen in the lungs at 40,000 feet if pure oxygen was being breathed would be only $-(47 + 36) = 58$ mm. Hg.

the mirror image of a clock face are performed less efficiently. Similar effects upon the mind are produced upon persons exposed to low oxygen pressures within a steel cabinet. The mental effects as pointed out by Barcroft are not unlike those caused by drunkenness. To quote his words,

"Alcohol affects different persons in different ways: so on my journeyings in high altitudes I have seen most of the symptoms of alcoholism reproduced. I have seen men vomit, I have seen them quarrel, I have seen them become reckless, I have seen them become garrulous, I have seen them become morose. I have seen one of the most disciplined of men fling his arms about on the ledge of a crevasse to the great embarrassment of the guide. I have seen the most loyal companion become ill-tempered and abusive to the point at which I feared international complications would arise."—Lessons from High Altitudes.

The effects of anoxia vary in severity and duration.

Complete prostration may follow the earlier symptoms. If the individual remains at the high altitude the symptoms pass off after a time, as he becomes acclimatized to the low oxygen tension.

CHANGES ASSOCIATED WITH ACCLIMATIZATION. At an altitude of 14,200 feet as at Cerro de Pasco where Barcroft and his party carried out their investigations the barometric pressure is around 440 mm. Hg. The partial pressure of oxygen is therefore about 92 mm. The oxygen tension of the alveolar air is not as far below that of the atmosphere as at sea-level, and varied among the greater number of the party from 55 to 60 mm. Hg. The closer approximation of the atmospheric and alveolar oxygen tensions at high altitudes is due to the increased breathing which results in a more effective ventilation of the air sacs. The increased respiration is brought about through the action of the lowered oxygen tension in the blood. The oxygen tension is slightly lower in the arterial blood than in the alveolar air which indicates that the passage of the gas is due purely to diffusion and not to an active secretion by the pulmonary epithelium. If this occurred, as has been suggested (Haldane), one would expect the arterial oxygen tension to be higher than that of the alveolar air. Alveolar carbon dioxide tension also, as a result of the increased pulmonary ventilation, is lower than that at sea-level; it varied in different individuals of Barcroft's party from 23 to 29 mm. Hg. At 14,200 feet the arterial blood is from 85 to 88 per cent saturated with oxygen (see fig. 149, p. 321).

A marked increase in the number of red cells (see p. 9) and a corresponding increase in hemoglobin content of the blood occur at high altitudes. The blood volume is also augmented. The natives of a mountainous regions have a red cell count of from 6 to 8 million per cubic millimeter. The greater quantity of hemoglobin of course raises the oxygen capacity of the blood and so tends to counteract its lowered oxygen saturation. That is, the *total* oxygen content of the arterial blood tends in spite of the low saturation to rise. Nevertheless, it may not be evident at first sight how a rise in the oxygen capacity is of advantage, for, blood of normal hemoglobin content even when only 80 per cent saturated possesses a quantity of oxygen which is quite adequate for the needs of the tissues. It has already been pointed out, however, that the important factor in supplying the tissues is the oxygen pressure gradient between the plasma in the capillaries and the tissue cells. So then, if there are a greater number of red cells each will be required to give up less of its oxygen store in passing through the capillaries to furnish a given quantity of oxygen (see anoxia due to anemia, p. 359). Consequently the saturation and the oxygen tension of the venous blood will be maintained at a higher level than otherwise would be possible. This means that the mean intracapillary oxygen pressure will also be higher, and as a result the tissues are more effectively supplied with oxygen.

The reduction in the alveolar carbon dioxide results in a corresponding decrease in the carbon dioxide tension of the arterial blood. The ratio $H_2CO_3/NaHCO_3$, which tends to be altered by the loss of carbon dioxide, is adjusted by a decrease in the excretion of acid and ammonia in the urine, a consequent lowering of the "alkali reserve" and depression of the CO_2 dissociation curve (p. 338). The actual pH of the plasma changes little if at all. Up to about 12,000 feet if any change occurs it is toward the alkaline side; above this level the blood reaction shows little further change or tends to return to normal. Lactic acid, which was thought at one time to be produced in excess as a result of the anoxia is actually formed in smaller amounts at high altitudes than at sea-level. Even during severe exercise at 15,000 feet and higher altitudes the lactic acid concentration in the blood is lower than during exercise of comparable severity at sea-level.

Barcroft and his party observed a shift to the left in the oxygen dissociation curve of hemoglobin, i.e., the affinity of hemoglobin for oxygen

was increased. The shift in the dissociation curve is ascribed by Barcroft to an increased alkalinity of the *interior of the red cell*. This increased alkalinity is in turn a direct result of the rise in the number of red cells. The buffering power of the blood is increased through the greater facility offered for the action of the "chloride shift" mechanism (p. 339). In other words, when a given amount of carbon dioxide is liberated by the tissues it is distributed among a greater number of red cells than under normal circumstances; therefore, the alkalinity of each cell is reduced to a proportionately less extent. There have been conflicting reports concerning this question of the shift in the oxygen dissociation curve. Some observers have been unable to confirm Barcroft's finding, while others claim that a shift to the right occurs. The truth appears to be that up to about 14,000 feet the affinity of hemoglobin for oxygen increases, but at higher levels the dissociation curve tends to assume the form found at sea-level, and at altitudes of 19,000 feet there is a definite shift to the right.

One might suppose that an increased circulation rate would be an important adjustment to the rarefied atmosphere whereby an adequate oxygen supply to the tissues would be maintained, but except for a temporary increase during the first few days no change in cardiac output occurs at altitudes of less than 14,000 or 15,000 feet. Above 15,000 feet the greater degree of anoxia results in an increase in the minute volume of the heart. Before acclimatization, the pulse rate during rest increases by from 15 to 20 beats per minute at altitudes between 15,000 and 18,000 feet. At greater altitudes, especially in persons in poor physical condition, the rate may increase above the normal. The acceleration of the pulse, according to Barcroft, is a signal of distress flown by the heart laboring under the effects of the anoxia, and not an indication of an increased minute volume. The blood pressure shows little or no change up to 15,000 feet; a small rise may occur at higher altitudes. For the effect of anoxia on the coronary circulation, see p. 279).

In the Andean expedition the diffusion coefficient (p. 314) of oxygen was not found to be increased to more than a slight extent during acclimatization yet those members of the party who had high diffusion coefficients to start with suffered less from mountain sickness than those in whom the coefficient was low.

Those who have lived all their lives at very high altitudes (around 14,000 feet) have a larger vital capacity than dwellers at sea-level. Barcroft reports that a native of Cerro de Pasco of 5 feet, 3 inches in height had a chest of a man of 6 feet. Moderate altitudes—up to about 7500 feet appear to have little or no effect upon the chest development.

Though anoxia is the most serious effect of high altitudes with which the mountain climber or aviator has to contend, rapid ascents, as by airplane, cause other important physiological disturbances which should be mentioned, namely, (1) expansion of gases in the gastro-intestinal tract, (2) aeroembolism and (3) pressure disturbances in the ears (p. 1044).

Expansion of gases in the gastro-intestinal tract. Like the gases of the atmosphere those in the stomach and intestine increase in volume in proportion to the reduction in pressure. Gas having a volume of 1 liter at sea level expands to 2 liters at the pressure (375 mm. Hg) existing at 18,000 feet, to 4 liters at 34,000 feet and to 6 liters at 42,000 feet (pressure 128 mm. Hg). Distension of stomach and intestine will result unless the abdomen is supported by a belt or by other means, or the gases are freely evacuated. In rapid ascents distress or even severe pain results if there is any hindrance, as by an obstruction in the colon, to the ready passage of flatus.

Caisson disease—Compressed air illness—Aeroembolism—"the bends"

Caisson disease and the corresponding condition that occurs during rapid ascents to high altitudes may be conveniently described here. Caisson disease occurs in deep sea divers or workers in caissons when they pass too quickly from the high pressure in which they have been confined to the ordinary pressure of the atmosphere.

When an animal is subjected to high atmospheric pressures the amount of the respiratory gases in the blood plasma and tissues increases in proportion to the raised partial pressures of these gases in the alveolar air. Very high pressures are well tolerated and no harm is caused by the increased amount of oxygen or nitrogen provided that they remain in solution.

The cause of the symptoms in Caisson disease are the bubbles of gas which form when the atmospheric pressure is suddenly lowered. These bubbles which are composed mainly of nitrogen act as emboli (*aeroembolism*) and the symptoms produced depend on the site where such emboli lodge—lungs, brain, heart, anterior or posterior spinal roots, etc. There may be extensive capillary hemorrhage and the frothing of the blood may interfere with cardiac action and with the flow of blood in the blood vessels. The amount of gas retained by an individual during the compression is proportional not only to the partial pressure of the gas but also to the amount of fatty tissue in which nitrogen is selectively soluble. Symptoms are not

produced unless the *excess* pressure is more than $1\frac{1}{2}$ atmosphere, however rapid is the rate of decompression or however long is the exposure to the higher pressure. Apparently the supersaturation of the tissues is not great enough and the volume of nitrogen liberated upon decompression is therefore not sufficient to form bubbles or at any rate to cause damage.

Aeroembolism can be avoided by slow decompression, the excess nitrogen being then gradually eliminated in the expired air. But slow decompression is inconvenient and tedious. The fact just mentioned that rapid decompression from a pressure of a little over 2 atmospheres does not cause symptoms suggested to Haldane and his associates that halving the pressure whatever its height, i.e., a reduction from 4 atmospheres to 2 or 6 to 3 could be carried out rapidly and with safety. This is the basis of the method of decompression now generally employed. Decompression is carried out in stages or steps rather than continuously, the air pressure to which the subject is exposed at each stage being just half the pressure at the preceding stage.

In *military airplane flights* the airman may be required to ascend to upwards of 30,000 feet (226 mm. Hg) within a few minutes. He is then subjected to rapid decompression, not, as is the deep sea diver, from a high pressure to atmospheric pressure, but from atmospheric pressure to a pressure of about $\frac{1}{2}$ of an atmosphere. But the same general principles apply and similar results follow as those outlined in the preceding section. A reduction in pressure from 1 atmosphere to $\frac{1}{2}$ of an atmosphere would correspond to a reduction from 3 atmospheres to 1 atmosphere. At 20,000 feet (350 mm. Hg) the pressure is little more than halved and aeroembolism would not be expected to occur. The effects of aeroembolism in flyers take the form most commonly of severe pain in one or more of the large joints (air-bends), itching of the skin or cutaneous sensations of heat or cold. Other more serious symptoms, e.g., paralysis due to the formation of bubbles in the spinal cord or brain, intense burning pain in the chest, or pulmonary edema may sometimes occur. The symptoms are, however, rarely as severe as those occurring in compressed air illness; the effects are not, as a rule, permanent and fatalities seldom result. They are quickly relieved in most instances by descending at once to lower levels. Aeroembolism is rare even with very rapid decompression (equivalent to ascents of 12,000 feet per minute) at altitudes below 30,000 feet. But above this apparently critical level they may result from a rate of ascent of only 200 feet per minute. The rate of ascent necessary to induce aeroembolism becomes progressively slower with increasing altitude; at 40,000 feet bends may result from a rate of only 80 feet per minute. The most effective way to prevent or diminish the effects of rapid decompression is to have the airman breathe pure oxygen or an oxygen-helium mixture (oxygen 21 per cent, helium 79 per cent) for a couple of hours

before the flight and thus induce the elimination of nitrogen from his tissues. Exercise also encourages the elimination of nitrogen.

ANOXIA DUE TO ABNORMALITIES OF THE PULMONARY MECHANISM

PNEUMONIA

In *lobar pneumonia* the oxygen saturation of the arterial blood varies in different cases from normal to less than 70 per cent. The signs and symptoms of anoxemia usually appear when the saturation is around 85 per cent. Cerebral symptoms, e.g., sleeplessness and delirium, cyanosis and dyspnea increase with the oxygen desaturation and a saturation of less than 80 per cent is associated with a very high mortality. In 33 cases reported by Stadie with a saturation as low or lower than this only 1 recovered. In lobar pneumonia the carbon dioxide content of the arterial blood is reduced on the average by about 15 per cent (Meakins and Davies). The "alkali reserve," however, is normal or only slightly reduced, the carbon dioxide dissociation curve not differing significantly from the normal. The blood pH may in some cases be shifted slightly toward alkalinity. From these findings it appears that there exists a partially compensated alkalosis, induced by the hyperventilation (blowing off of carbon dioxide). In severe cases the excessive elimination of CO₂ may cause a rise in the respiratory quotient to above unity. The increased ventilation of the alveoli also increases the percentage of oxygen in the alveolar air but this fact cannot, as we shall see presently, increase appreciably the oxygen in the arterial blood.

In *bronchopneumonia* a higher degree of oxygen desaturation of the arterial blood is usually present than in the lobar type. The cyanosis may be extreme. There is often *retention* of carbon dioxide when a rise in plasma bicarbonate results, to compensate, in part at least, the gaseous acidosis. The carbon dioxide content of the arterial blood may be 80 volumes per cent or more and the carbon dioxide dissociation curve well above the normal level.

The causes of the anoxia (anoxemia) in pneumonia

The main factors concerned in the production of the anoxemia are (a) the passage of blood through unaerated portions of the lung and (b) shallow breathing. The oxygen unsaturation is not due to any change in the hemoglobin itself (e.g., the formation of methemoglobin) since the blood of pneumonia patients has a normal oxygen capacity.

The oxygen dissociation curve at a given carbon dioxide tension is not appreciably different from that of normal persons.

In *lobar pneumonia* during the stages of engorgement and red hepatization the alveoli of the affected portion of the lung are poorly aerated. Mucus blocks the bronchioles and the *air spaces* are filled or their walls coated with exudate. But a large proportion of the vessels of these unaerated regions are still pervious. Consequently blood traversing such areas must remain poor

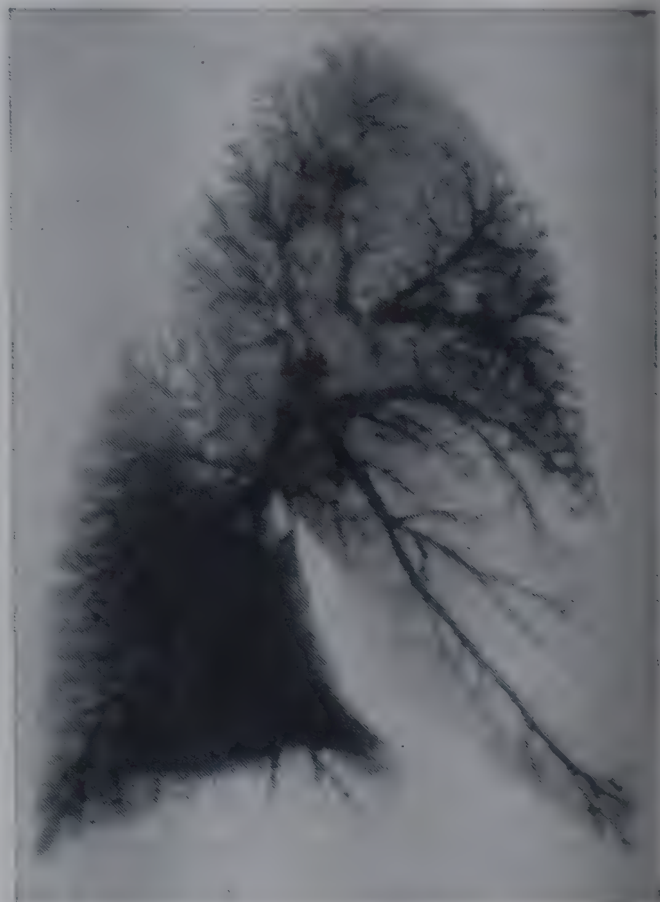


FIG. 163. X-ray photograph of lung (injected with barium) from a case of lobar pneumonia (after Gross). *Upper right hand area.* Consolidated area—red hepatization. The main vessels are constricted and the fine vascular structure is less dense than in the normal lung. *Lower right hand area.* Consolidated area—gray hepatization. The main vessels are patent but the fine vessels have been occluded. *Lower left hand area.* Healthy portion of lung except for compensatory congestion; the vessels are dilated.

oxygenated or entirely venous. This blood with a low oxygen saturation and a high carbon dioxide content mixes with blood which has passed through aerated regions. The general arterial blood therefore has its oxygen saturation reduced in proportion to the amount of unsaturated blood with which it is mixed (see also Shunt, p. 371). When the pneumonic area passes into the stage of gray hepatization the vessels of the affected lobe become obliterated to a large extent and the pulmonary blood then passes through aerated regions (fig. 163). That is, the arterial blood is no longer

initiated by blood from non-aerated areas. Therefore in a typical case of lobar pneumonia when the disease is confined to a single large area and the breathing is not shallow there is little anoxemia at this stage. If however, bronchopneumonic areas co-exist, the respiratory functions will be affected as described below. (See Oxygen Therapy, p. 375.)

In *bronchopneumonia*, patches of lung tissue are cut off from their air supply. The fine bronchioles become plugged with mucus, groups of alveoli become filled with exudate and the alveolar walls are edematous and thickened. Yet, obliteration of the vessels to any great extent does not occur. Blood continues to flow through unaerated areas. This blood which is highly venous, mixing with that from aerated alveoli lowers the saturation of the general arterial blood.

SHALLOW BREATHING. In pneumonia the breathing is frequently very rapid and shallow. Instead of the tidal air being around 500 cc. as in health it may be reduced to 250 cc. or less. It will be recalled that 150 cc. are required to fill the anatomical dead space, therefore only 100 cc. will enter the air sacs of the healthy parts of the lung. We have seen that the expansion of the lungs is not equal in all its parts (p. 490). The alveoli towards the hub of the radiating rays expand less than those near the periphery. Those parts, such as the apex, which are indirectly expanded have even in health a tendency to be ventilated less than those which are directly expanded. In shallow breathing, these differences are greatly exaggerated. Though the volume of the tidal air is only half the normal, the total quantity of air breathed per minute (minute volume) is, as a result of the increased respiratory rate, much greater than normal. Since a proportion of the alveoli are very poorly ventilated or not at all, owing to the unequal expansion of the lung, those in other areas are over-ventilated. The O_2 tension in the latter is therefore raised. But so far as the oxygenation of the blood is concerned the over-ventilation of some alveoli cannot make up for the under-ventilation of others. We know that the hemoglobin is nearly saturated already at the ordinary alveolar oxygen tension of 100 mm. Hg (see footnote p. 317). As already mentioned the dissociation curve of hemoglobin in pneumonia does not differ appreciably from that in health and the most therefore that could be expected from a rise in the alveolar O_2 tension would be an increase of less than 5 per cent in oxygen saturation of the blood traversing over-ventilated regions and a slight increase in the amount of O_2

held in simple solution. In other words, the blood flowing through the poorly ventilated parts of the lung will have a low saturation since the O_2 tension is low, while that flowing through the over-ventilated parts will be little above the normal. The net result will be a low oxygen saturation of the mixed arterial blood.

Matters are different in the case of CO_2 elimination. The shape of the CO_2 dissociation curve which shows a progressive slope throughout the entire range of CO_2 tensions is quite unlike that for oxyhemoglobin (fig. 164). The greater total ventilation results in a lowering of CO_2 tension in the over-ventilated parts of the lung and, conse-

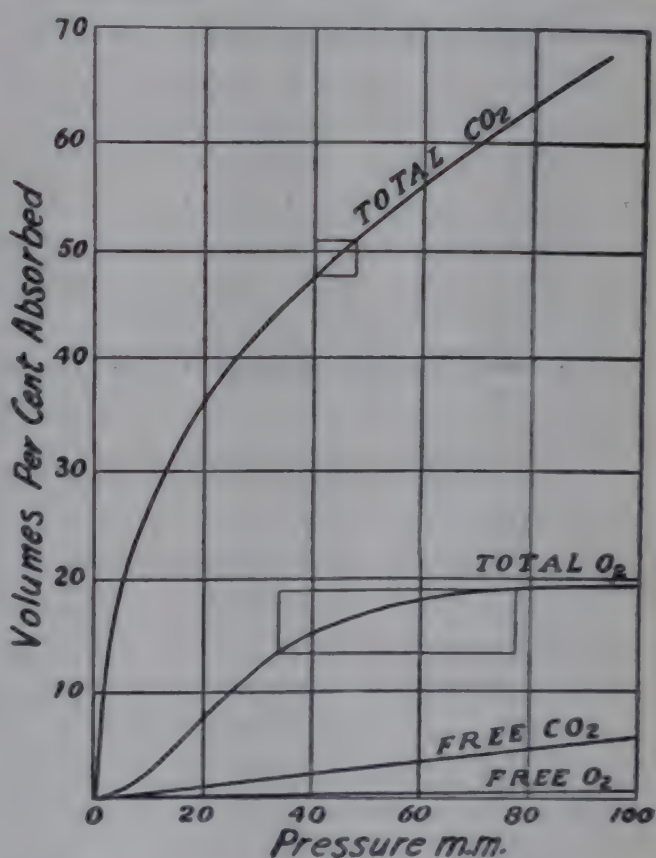


FIG. 164. Carbon dioxide and oxygen dissociation curves. The small rectangles indicate the extent of the variation of the O_2 and CO_2 of the subject's blood when at rest. (From L. J. Henderson.)

quently, in a "blowing off" of CO_2 from the blood circulating through these regions. CO_2 is retained in the blood circulating through poorly ventilated regions. In the patient with lobar pneumonia the amount of CO_2 blown off may exceed that retained; the net result will be a lowering of the CO_2 content of the arterial blood. In bronchopneumonia a larger proportion of the pulmonary blood circulates through non-aerated areas. As a consequence, CO_2 retention is greater, and a normal or a higher than normal CO_2 content of the blood is more usual.

Haldane, Meakins and Priestley produced anoxemia in normal persons by having them breathe into an apparatus which reduced the

volume of the tidal air. As the depth of the breathing became reduced the respiration increased to 100 or more per minute. The CO_2 percentage of the alveolar air fell and the O_2 percentage rose. The shallow breathing artificially induced in this way resembles that seen in pneumonia and other diseased conditions. The administration of oxygen abolished the anoxemia.

The cause of shallow breathing in pneumonia. Pleuritic pain, by restricting the respiratory excursions, may result in this type of breathing. In other instances it appears to be of a reflex nature resulting from the inflammatory process which, through a reduction in the distensibility of the pulmonary tissue, exalts the sensitivity of the afferent vagal endings in the alveolar walls. Thus the inspiratory movement is terminated before a full excursion has been completed (see Hering-Breuer reflex, p. 345). In support of a reflex origin the experiments of Dunn and of Binger, Brow and Branch may be mentioned who produced this type of breathing in animals by the intravenous injection of potato starch granules. These, acting as small emboli, plugged the pulmonary capillaries. The rapid shallow breathing was immediately abolished by section of the vagi or prevented if the nerves had been cut before the injection. Breathing a mixture rich in carbon dioxide with intact nerves also restored the respiratory rate and depth to normal—the action of carbon dioxide upon the respiratory center itself overcoming the afferent nervous influence. Also, in pneumonia it has been found that oxygen inhalations, even though they may restore the oxygen saturation of the arterial blood to normal, do not necessarily abolish the shallow breathing—further evidence for the existence of a nervous element in the production of this type of breathing. Shallow breathing may also result from other diseases involving the alveoli, e.g., inflammation by irritant gases (phosgene and chlorine), pulmonary edema, miliary tuberculosis and pulmonary emboli, which would be expected to stimulate afferent nerve endings. It also occurs in certain nervous states, hysteria, certain forms of neurasthenia and sometimes in encephalitis lethargica, but is not seen in lesions involving the bronchi or bronchioles alone, e.g., bronchitis and asthma.

Severe anoxemia, however produced, tends itself through its damaging effect upon the respiratory center to induce rapid shallow breathing, and in any event will exaggerate this type of breathing, since it also tends to increase the sensitivity of the Hering-Breuer reflex. Thus a vicious circle—

shallow breathing inducing anoxemia and the latter reacting to enhance the former—is set up. Shallow breathing induces one of the gravest types of anoxemia, since the cardiovascular system, as well as suffering from oxygen want, is seriously affected by the excessive loss of carbon dioxide (see p. 250). Owing to the narrowed state of the cutaneous vessels the cyanosis is of the pale leaden-gray type (p. 375) and if the anoxia is not relieved, failing circulation adds to the oxygen want (anoxia of the stagnant type). The acapnia would also tend to magnify the oxygen want of the tissues for, as we have seen, the hemoglobin gives up its oxygen less readily at low carbon dioxide tensions.

ASTHMA

This is a paroxysmal disease in which acute oxygen want is caused by a spasm of the smooth muscles of the finer bronchioles. Edema of the bronchiolar mucosa is probably also present. The alveoli are poorly ventilated and some may be completely cut off from their air supply. The high percentage of carbon dioxide and low percentage of oxygen in the alveolar air result in a low oxygen saturation of the arterial blood and the retention of carbon dioxide. The gaseous acidosis is met by the excretion of a highly acid urine and a rise in the "alkali reserve." An intense plum-colored cyanosis develops. The continued stimulating effect of oxygen want and carbon dioxide excess upon the respiratory mechanisms causes violent hyperpnea.

Difficulty is experienced both in inspiration and expiration but since there is a natural tendency for the bronchioles to narrow during expiration and dilate during inspiration the greatest respiratory effort is exerted during expiration. The respiratory muscles contract with great force and the accessory muscles of respiration are brought into play. The expiratory muscles compress the chest and the abdominal muscles contract in the attempt to squeeze the air from the lungs. The intrapulmonary pressure is greatly elevated and the air escapes through the constricted tubes with a distinct wheezing sound. Owing to the difficulty and prolongation of the expiratory phase normal deflation of the lungs cannot occur before the next inspiration ensues. The lungs, therefore, remain almost maximally expanded even at the end of expiration. That is, during the asthmatic paroxysm a very large volume of residual air is present in the lungs (fig. 165). The volume of the tidal air is greatly reduced and corresponds to the vital

capacity at the moment. Since the subject is already exerting the greatest inspiratory and expiratory efforts of which he is capable there can be no supplemental or complemental air. The changes in volume of the over-distended lung are small and not commensurate with the excursions of the thoracic walls. As a consequence, the high value of the intrathoracic negative pressure induced during inspiration causes the structures at the root of the neck to be drawn toward the thoracic cavity to take up the space which the

is fixed in an elevated position, resembling the normal chest in full inspiration. The sternum is prominent and the ribs more horizontal than normally. The anteroposterior diameter of the thorax is as great or greater than the lateral, the chest assuming the so-called barrel shape.

The *sputum* in asthma contains spirals of delicate fibrils (Curschmann's spirals) formed of bronchiolar secretion, diamond shaped crystals (Charcot-Leyden crystals) and eosinophil cells. A substance possessing a histamine-like action has been demonstrated in the sputum by Knott. The blood in asthma shows a great increase in the eosinophil cells (eosinophilia). The effect of the asthmatic paroxysm upon the heart is that of partial asphyxia. A-V conduction may be depressed as shown by some lengthening of the P-R interval in the electrocardiogram or premature beats may occur. The attack appears to cause no permanent damage to the cardiovascular system.

Causation

Asthma often shows a strong hereditary tendency. The bronchiolar spasm may be (a) of a *reflex nature* and due to the stimulation of hyper-sensitive afferent vagal endings in the larynx, or of trigeminal fibers by some nasal abnormality; the bronchoconstrictor impulses travel via efferent vagal fibers, (b) an *allergic phenomenon*, i.e., the result of sensitization to some foreign protein. This is the most common cause of the condition. It is then frequently associated with other allergic conditions, e.g., hay fever, urticaria or eczema either in the patient himself or in members of his family. The foreign protein may be inhaled. Pollens of various grasses and flowers, the dandruff of animals, e.g., horse, cat or dog, or feathers are among the most common excitants; the exciting cause may be some kind of food or the protein of bacteria within the respiratory tract itself may be responsible. The sensitivity of certain individuals to foreign proteins presents many features resembling those of anaphylactic shock in animals. The two conditions are probably in some way closely related. Sudden death may result from the injection of horse serum (e.g., diphtheria antitoxin or anti-tetanic serum) into an asthmatic subject. A guinea pig when injected with a protein to which it has previously been sensitized dies rapidly from anaphylactic shock. The bronchiolar muscle is strongly contracted. The air is trapped so that the lungs are maximally distended and do not collapse when the thorax is opened. Even when the pulmonary tissue is deeply incised the air does not escape

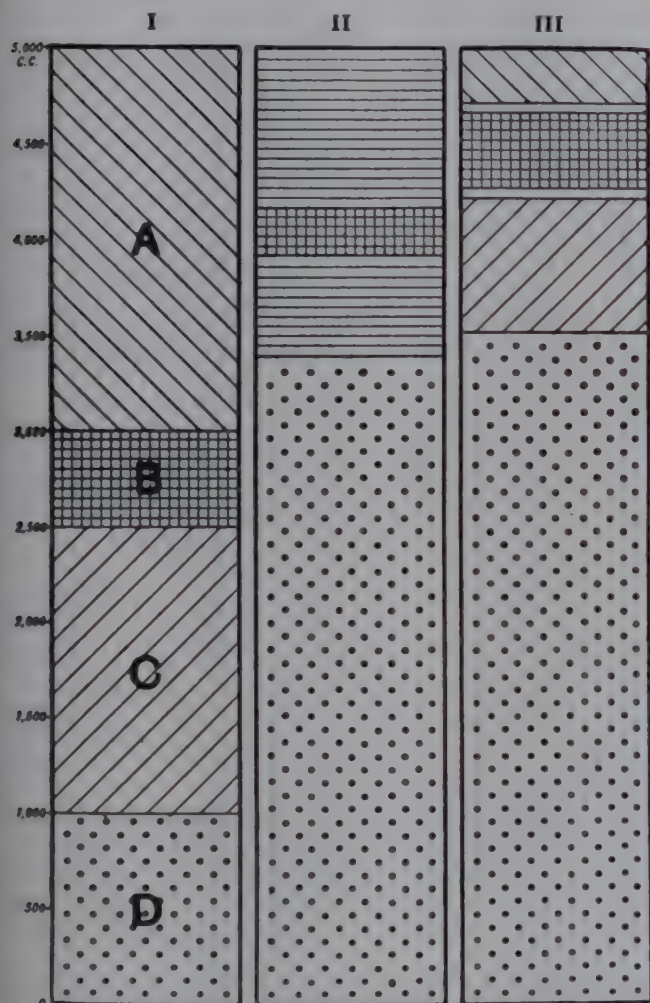


FIG. 165. Diagram showing subdivisions of the lung air in asthma (II) and emphysema (III) compared with the normal (I). A, complemental air; B, tidal air; C, supplemental (reserve) air; D, residual air. The horizontal lines above and below the area representing tidal air in II and III indicate the extent of the respiratory movements. (After Coke.)

lungs are unable to fill. These structures are expelled again during expiration. The veins of the neck and face become engorged. Restricted movements of the lung also greatly reduce the effect of mechanical mixing upon the lung air, the slower process of diffusion being depended upon to a larger extent for the freshening of the alveolar air.

Repeated asthmatic attacks during early life, while the thoracic framework is still soft, produce a characteristic deformity of the thorax. The chest

from the distended lung. This manifestation of anaphylaxis is associated with, perhaps due to, the liberation of histamine into the pulmonary circulation. Several groups of workers agree that histamine appears in the blood promptly after the administration of the antigen and persists for a brief interval. It is well known that anaphylaxis and histamine administration produce almost identical effects in the guinea pig (fig. 166). Histamine producing bacteria have been reported in the bronchial secretions of asthmatics.

The bronchiolar movements are not dependent entirely upon extrinsic autonomic nerves, but are under the control of an intrinsic nervous mechanism.

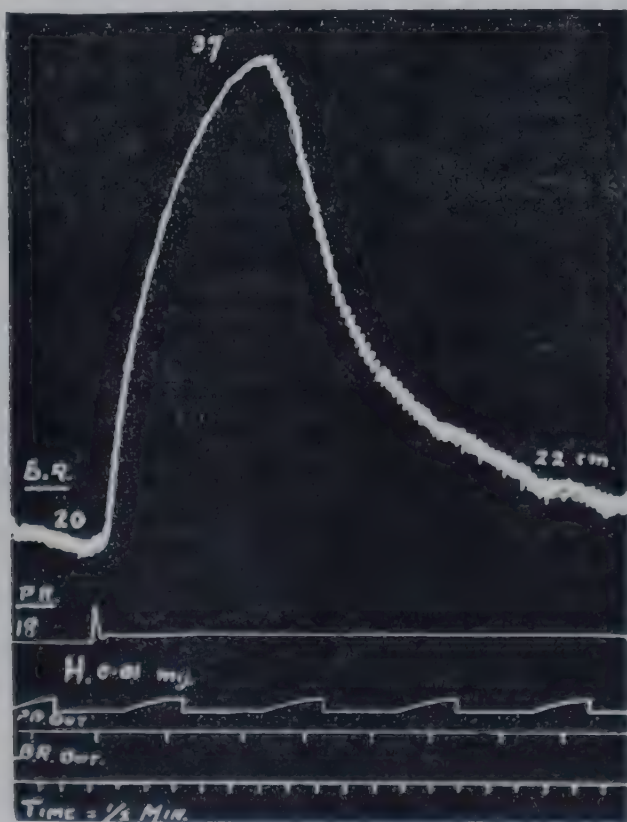


FIG. 166. Guinea-pig. Reaction of bronchial muscle to 0.01 mg. histamine. (After Thornton.)

Daly found in experiments with perfused isolated lungs that varying the bronchial circulation, through which the pulmonary nerves and ganglia are supplied, caused changes in pulmonary ventilation. He suggests that a disturbance of the intrinsic nervous control of the bronchioles through alterations in its blood supply may play an important rôle in some types of asthma. Attention is thus directed to abnormal vasomotor influences rather than to factors—nervous or humoral—acting directly upon the bronchial musculature.

The treatment of asthma resolves itself into the relief of the paroxysm and the removal of the underlying cause. Adrenaline or ephedrine acts by inhibiting the bronchiolar muscle during the attack. Atropine paralyzes the broncho-constrictor

(vagal) fibers. Of the three drugs, adrenaline is the most effective. In the allergic form of the disease every effort is made to identify the offending protein.

CHRONIC EMPHYSEMA

(Greek *em* + *physema*, a blowing)

The lungs in emphysema are in a state of extreme distension as a result of the enlargement of the air sacs. The latter, however, show fewer alveoli in their walls owing to the atrophy of the inter-alveolar septa. Contiguous air sacs within a lobule coalesce or even adjacent lobules may fuse to form large air spaces. For this reason the total respiratory surface is reduced. The alveolar and capillary walls become thickened and the interstitial pulmonary tissue increased. Many capillaries become occluded. The pulmonary elastic tissue is reduced in amount so that the lungs, when removed from the thorax, do not collapse normally but remain in an overexpanded state. The peripheral lobules, which in health expand to the greatest extent, are those mainly affected in emphysema, the enlarged lobules appearing as blebs upon the surface of the lung.

The chest is what is known as barrel-shaped. The ribs are more horizontal than normally, the thoracic spine is bowed backwards (kyphosis) so that the anteroposterior diameter of the chest is as great as or exceeds the transverse. The position of the chest is one of nearly full inspiration. The mid-position of the diaphragm is at a much lower level than usual and its excursions above and below this level are restricted. The respiration is therefore mainly costal. In some instances the diaphragm is practically fixed or indeed may be drawn up during inspiration (paradoxical movement). As in the paroxysm of asthma the residual air is 2 or 3 times the normal and the complementary air is reduced. The tidal air is normal or only moderately reduced and the vital capacity (fig. 165) is lowered by from 20 to 60 per cent. Owing to the loss of the elasticity of the lung, expiration is no longer simply a passive movement but is aided by a forcible contraction of the expiratory muscles. When the patient is asked to make a deep inspiration he does not expel all the air during the next expiration. A series of respirations occur before the chest returns to its original size. Furthermore, he cannot expel nearly as large a volume of reserve (supplemental) air immediately after a deep inspiration. These phenomena are due to the fact that the inelastic lungs have been over-

stretched and are brought back to their original volume with difficulty.

In emphysema there are anoxemia and retention of carbon dioxide. The oxygen saturation of the arterial blood runs from a little below normal to around 85 per cent. The carbon dioxide tension in the alveolar air in well marked cases is from 50 to 60 mm. Hg (7 to 8 per cent) and the carbon dioxide content of the arterial blood correspondingly high.

The cause of the impaired gaseous exchange is not altogether clear. Thickening of the alveolar and capillary walls has been considered to be a factor. Yet if this were so one would not expect the retention of carbon dioxide which, owing to its greater solubility (30 times that of oxygen) has a much higher rate of diffusion through the pulmonary membrane, to be so much more pronounced than the anoxia. The sharp rebound at the end of inspiration which occurs in the healthy lung causes mechanical mixing of the lung air and is an important factor in the efficient ventilation of the alveoli. The absence of this effect in the emphysematous lung and its greater dependence, in consequence, upon the slower process of diffusion is probably an important factor leading to the defective aeration of the blood. According to Christie, the impaired gaseous exchange is due mainly to the fact that, as a result of the loss of elasticity, the intrathoracic pressure is not distributed evenly throughout the lung. As a consequence, the outlying alveoli which are largely functionless with obliterated vessels are ventilated to a greater extent than the relatively healthy ones more centrally placed. Owing to the shapes of the respective dissociation curves such under-ventilation of the functioning alveoli will tend to have a greater effect in preventing the elimination of CO_2 than in interfering with the absorption of oxygen. Another factor which is probably of importance is the slower rate of diffusion of CO_2 , owing to its larger molecule, in the alveolar air.

The red cell count, hemoglobin percentage, and consequently the oxygen capacity of the blood, are increased above the normal in emphysema. The cyanosis (p. 372) is often pronounced, yet the patient's dyspnea is less than might be expected from his color, often startling, and from the carbon dioxide retention which exists. This is explained by the well established fact that in emphysema the respiratory center is relatively insensitive to carbon dioxide. A normal person when breathing a carbon dioxide rich mixture (8 per cent) increases his pulmonary ventilation by 300 per cent

or more; the breathing of the emphysematous patient on the other hand shows relatively little change as a result of breathing a much stronger mixture (see fig. 167).

Causation

Two factors are concerned in the production of emphysema (a) reduction in the elastic tissue of the lung and (b) increased distention of the alveolar spaces.

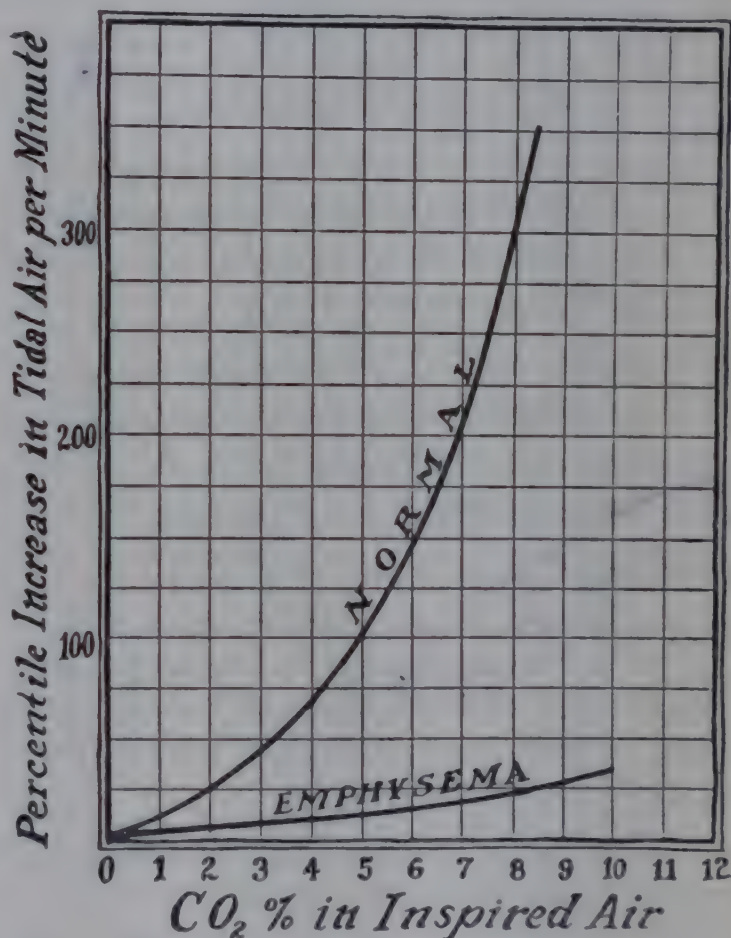


FIG. 167. Chart showing the percentile increase in tidal air per minute as the percentage of inspired carbon dioxide is raised. Note that when the normal subject inspires air containing 8 per cent carbon dioxide, the tidal air is increased about 300 per cent, whereas in the emphysematous subject it is increased only about 25 per cent. (After R. W. Scott.)

It is very questionable whether, in the absence of some abnormality of the lung tissue itself, emphysema can result from increased intrapulmonary pressure, such as occurs in those following certain occupations, e.g., glass blowers and the players of wind instruments. The study of groups of men following such occupations does not indicate that emphysema is produced in this way. Emphysema has, however, been induced in animals by stenosis of the trachea or bronchi or by the insertion of a valved apparatus into the trachea which allowed the free ingress of air but offered an obstruction to expiration. It is probable that

in these instances the persistently high intra-alveolar pressure by stretching the lung structures during *inspiration* first caused atrophy of the elastic tissue. During inspiration the air spaces are dilated by the negative pressure upon their outer surfaces. The trapped inspired air causes an ever-increasing distending pressure to be exerted upon the alveolar walls. Inasmuch as the intrathoracic pressure is "less negative" during expiration, a reduction rather than an enlargement of alveolar capacity would result at this time (see p. 297). Asthma and chronic bronchitis⁴¹ which frequently are forerunners of emphysema also, probably, exert their damaging effect upon the alveolar structure during the inspiratory phase. In the former condition the spasm of the bronchiolar muscle exerts a valve-like action (see p. 307). In chronic bronchitis mucous plugs would act similarly. Coughing, it has been supposed, places a strain upon the alveolar walls. But during the phase of coughing when the glottis is closed the alveolar walls are supported. When the glottis opens, the air escapes from the alveoli if the obstructing material has been dislodged, and no strain upon the alveolar wall would result. If, however, the air remains entrapped its sudden re-expansion (rebound), as the pressure in the surrounding pulmonary tissue falls at the end of a cough, may injure the alveolar membrane and start the emphysematous process.

What may be termed a physiological or *compensatory* emphysema occurs when part of the pulmonary surface is reduced as by the collapse of a part or the whole of one lung. This is more in the nature of an hypertrophy. A similar enlargement of both lungs occurs at high altitudes.

A type of emphysema also occurs in the elderly—*senile* or *postural emphysema*—and is secondary to the change in the shape of the thorax which becomes more barrel-shaped and increased in capacity. The lungs enlarge to fill the increased space. This condition is associated with few symptoms. There is little reduction in the vital capacity and the oxygen saturation of the arterial blood is practically normal.

COLLAPSE OF THE LUNG OR ATELECTASIS

(Gk *ateles*, incomplete; *ektasis*, distention)

Any condition which lowers the pressure (atmospheric) within the alveoli or increases the pressure upon the lung surface, i.e., reduces the "negative" intrapleural pressure, may lead to collapse of the lung. Thus pleural effusions, pneumothorax, tumors, etc., pressing from without

or the isolation of the alveoli from their air supply by the obstruction of a bronchus will therefore result in collapse of the lung or of the portion of lung affected. Atelectasis is also the term applied to the condition in the newborn in which, as a result of the blockage of a bronchus or of a group of bronchioles by mucous secretion, or owing to weak inspiratory movements, a portion of lung fails to become distended with air.

When a bronchus or bronchiole in a previously distended lung is obstructed the imprisoned air soon becomes absorbed from the affected alveoli. Collapse of the air sacs cannot take place until this has occurred. Absorption is brought about in the following way, as pointed out by Henderson. The air in the isolated alveoli has a total pressure of 760 mm. Hg (p. 315). The partial pressures are in round numbers, O_2 , 100 mm.; N_2 , 570 mm.; CO_2 , 40 mm. and aqueous vapor, 47 mm. In the venous blood the total pressure is 703 mm., the nitrogen and aqueous vapor being the same as that of the alveolar air, but the partial pressure of oxygen is only 40 mm. and of carbon dioxide 46 mm. An interchange of the latter gases therefore occurs between the alveolar air and the venous blood. It might be thought that the imprisoned air would then be in equilibrium with the blood and no further absorption occur. But the alveolar air loses more oxygen than it gains carbon dioxide whereupon its volume is reduced. The atmosphere acting upon the body surface and through the yielding soft tissues compresses the air so as to maintain its total pressure practically constant at 760 mm. As a result of the absorption of oxygen the percentage and consequently the partial pressure of carbon dioxide and of nitrogen are increased. These gases now diffuse into the blood. The volume of the air is further reduced thereby but its total pressure still remains unaltered. The percentage and therefore the partial pressure of oxygen rises and more of this gas passes into the blood. The process continues in this manner until no air remains, and the walls of the original space are ultimately approximated by the pressure of the atmosphere. Air is absorbed from the pleural cavity or from any other closed cavity of the body in precisely the same way (Henderson and Henderson). The absorption of the air confined within the pleural cavity permits the lung, if the air pressure has caused its collapse, to re-expand (see also p. 31).

The collapse and shrinkage of the lung which results from blockage of a bronchus increases intrathoracic negative pressure, since the closed

Thoracic box is less completely filled. The diaphragm is therefore drawn upwards and uncollapsed portions of the lungs are expanded to a greater extent (compensatory emphysema) in order to fill the unoccupied space.

terial blood will be seriously reduced. Anoxemia, evidenced by cyanosis (p. 372) and dyspnea (p. 353) will result (fig. 168). These will be especially pronounced upon exertion since the unsaturation of the polluting venous blood will be thereby increased.

The congenital malformations responsible for this type of anoxia are:

(1) *Patent foramen ovale* through which a communication persists between the two auricles.

(2) *Patent ductus arteriosus (ductus Botalli)*. In the fetus the pulmonary artery after dividing into right and left branches is continued onwards to open into the aorta. Most of the blood leaving the fetal right heart takes the latter course since the lungs are unexpanded; only a small fraction passes through the right and left pulmonary arteries. At birth the expansion of the lungs diverts the blood from its prenatal course. Normally the ductus arteriosus gradually closes appearing in later life as a mere vestige (ligamentum arteriosum). If it fails to close a passage will be afforded for the transference of blood from the aorta to the pulmonary artery.

(3) *Defects in the interventricular septum*. According to Lundsgaard and Van Slyke about one-third of the venous blood must be shunted before cyanosis appears. The absence of this sign therefore does not preclude the existence of a congenital defect—for the quantity of shunted blood may be simply insufficient to produce a high degree of anoxia. It must also be remembered that the diversion of blood may be from left to right rather than the reverse and anoxia would not result. On account of the higher pressure on the arterial side this is what might be expected. Stenosis of the pulmonary artery, however, commonly co-exists with an open ductus arteriosus. This has the effect of raising the pressure on the right side and favoring the flow of venous blood into the arterial stream. In cases of patent foramen ovale the flow is usually from left to right. The development of a mitral lesion by raising the pressure in the pulmonary circuit may reverse the direction of a flow which had previously been from left to right.

The red cell count in congenital heart disease is frequently above the normal. The influence of this upon the degree of cyanosis is discussed on page 374 et seq.

CARBON MONOXIDE AND CYANIDE POISONING

CARBON MONOXIDE POISONING

References to carbon monoxide poisoning are contained in the earliest medical writings. This gas was used by the Greeks and Romans for the execution of criminals and as a means of committing suicide. Carbon monoxide is today the most important gaseous poison against which

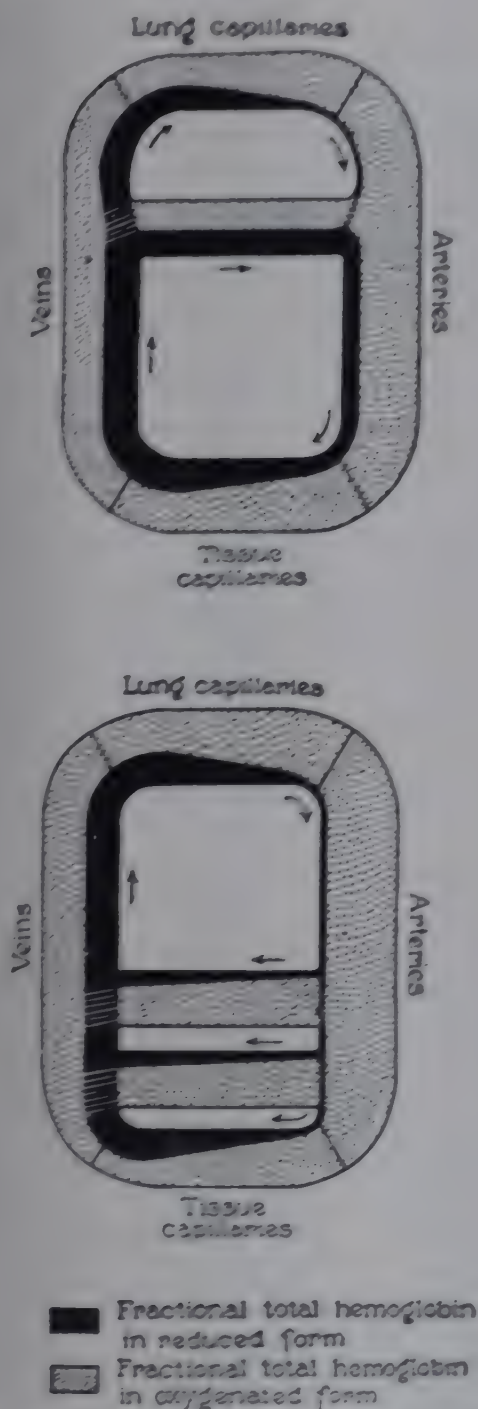


FIG. 168. Diagram (upper) showing the proportion of oxyhemoglobin to reduced hemoglobin in different parts of the circulation in an instance where a portion of the blood passes through unaerated channels (shunt) from the venous to the arterial system. Lower diagram presents a case in which the oxygen unsaturation of the blood is abnormally high in a part of the peripheral capillaries but normal in the arterial blood (stagnant type of anoxia). (After Lundsgaard and Van Slyke.)

SHUNT

It is clear that if a large proportion of the venous blood does not traverse the lungs but is short-circuited from the right to the left heart or directly to the aorta, the oxygen saturation of the ar-

physicians have to contend. During times of peace it accounts for more deaths than all the other gases combined. Carbon monoxide combines with the hemoglobin of the blood and thus renders it unavailable for oxygen carriage. This combination is represented by the following reversible equation:



The affinity of hemoglobin for carbon monoxide is approximately 300 times its affinity for oxygen.

Therefore we may substitute $\frac{300}{1}$ for the ratio

$\frac{\text{ACO}}{\text{AO}_2}$. While it can be shown that carbon monoxide

may seriously interfere with tissue respiration this is probably not an important factor in carbon monoxide poisoning since (1) the concentrations of the gas are seldom sufficient to affect the tissues and (2) the anoxia produced by the lack of oxygen carriage causes death before tissue respiration can be specifically affected by the gas. There are numerous ways of estimating the carbon monoxide content of air or blood. Carbon monoxide in air may be estimated gasometrically with a modified Haldane or with the Van Slyke apparatus. The color produced in blood by the carbon monoxide hemoglobin may be matched with that of a carmine solution and the amount of carbon monoxide hemoglobin estimated in this way (Haldane).

Recovery from carbon monoxide poisoning is usually complete when the exposure has not been too long or the concentration too high. It is important that the carbon monoxide hemoglobin should be broken up as soon as possible since injury to the tissues is produced by the anoxia. It is possible to displace the carbon monoxide by oxygen if the tension of oxygen is sufficiently high and that of carbon monoxide low. Mixtures with a high percentage of oxygen and from 6 to 7 per cent carbon dioxide which, as well as acting as a stimulus to the respiratory center reduces the affinity of carbon monoxide for hemoglobin, are used in the treatment of this condition. Intravenous injections of methylene blue have been advocated but are valueless. Methylene blue accelerates oxidation in the tissues; the difficulty in carbon monoxide poisoning, however, is not lack of oxygen utilization but deficiency in the carriage of oxygen by the blood. By forming methemoglobin the dye has actually just the opposite effect. Carbon monoxide, as well as its action in displacing oxygen from hemoglobin, has histotoxic properties, inhibiting the tissue respiratory enzymes.

This fact has no practical bearing, however, upon carbon monoxide poisoning in man, for the concentrations at which such action occurs is many times greater than could ever occur in the body.

CYANIDE POISONING

The mechanism of production of asphyxia by cyanide is quite different from that of carbon monoxide. There is no interference with oxygen carriage by cyanide but there is inhibition of tissue respiration. Cyanide apparently combines with one or more of the enzymes which are responsible for normal tissue respiration (see p. 323). It follows from this that any antidote for cyanide poisoning must have one of two actions. Either the cyanide must be removed or detoxified or the inactivated catalyst must be replaced. Methylene blue does act as a catalyst for certain biological oxidations and this led to its use as an antidote for cyanide poisoning. When methylene blue is given to the intact animal there is a marked rise in body temperature which is due to increased metabolism and not to diminished heat loss. The evidence is satisfactory that methylene blue will reverse the inhibiting effects of cyanide on cellular oxidations. This fact has been established from investigation on a great number of tissues. Sahlin in 1926 provided the first experimental demonstration that methylene blue antagonizes the action of cyanide in the intact animal. He used rats and the observation has been confirmed on other animals—dogs, rabbits, mice. The evidence suggests that methylene blue acts by removing the cyanide from tissue. Methylene blue and cyanide do not combine directly but methylene blue forms methemoglobin and the methemoglobin combines with the cyanide to form cyanmethemoglobin. The cyanmethemoglobin is relatively non-toxic and is broken down slowly, the detoxification probably being brought about by conversion by the cyanide to thiocyanate (Smith and Malcolm). Other substances which form methemoglobin (Hug; Wendel) such as sodium nitrite, amyl nitrite, pyrogallol, etc., are also effective in the treatment of cyanide poisoning. Such methods of course are limited by the quantity of hemoglobin that can safely be converted to methemoglobin.

A number of sulphur compounds have been found effective in cyanide poisoning. Chen, Rose and Clowes showed that sodium thiosulphate and sodium tetrathionate may protect dogs against as much as three lethal doses of cyanide.

CYANOSIS

(Greek, *cyanos*, blue)

Cyanosis may be defined as the diffuse, dusky or bluish color imparted to the skin by the presence in the blood of the superficial capillaries (subpapillary venous plexus, see p. 266) of re-

duced hemoglobin above a certain definite amount.³ It seems scarcely necessary to state that the retention of carbon dioxide in the blood has no *direct* effect upon the production of cyanosis. The blue color of the skin depends fundamentally upon the *absolute* amount of reduced hemoglobin in the capillary blood and *not* upon the *relative proportions* of reduced and oxyhemoglobin. For example, in anemia the hemoglobin content of the blood may be only 20 per cent of the normal. In the capillary blood all of this might be in the reduced form yet cyanosis would not result, since the absolute amount of reduced hemoglobin (i.e., "blue pigment") would be insufficient to produce any blue discoloration. On the other hand, in polycythemia the hemoglobin may be 100 per cent above normal. Cyanosis will occur when the hemoglobin of the capillary blood is only 20 per cent reduced, for the absolute concentration of reduced hemoglobin will then be raised to threshold value. The greater quantity of the bright-colored oxyhemoglobin present exerts little or no influence; that is, it does not, as might be expected, tend to neutralize the color effect of the reduced hemoglobin.

Normal blood contains about 15 grams of hemoglobin per 100 cc. Lundsgaard found that the capillary blood must contain approximately 5 grams of reduced hemoglobin per 100 cc. before cyanosis will appear. Three-fourths gram of hemoglobin takes up 1 cc. of oxygen. So, blood containing 15 grams of hemoglobin per 100 cc. can take up $\left(\frac{15}{0.75} = \right)$ 20 volumes per cent of oxygen. Five grams of hemoglobin absorb $\left(\frac{5}{0.75} = \right)$ 6.7 cc. of oxygen, i.e., 5 grams of reduced hemoglobin are formed when 100 cc. of blood gives up 6.7 cc. of oxygen. Therefore cyanosis would be expected to appear when the blood in the capillaries has lost on the average 6.7 volumes per cent of oxygen, that is, when the hemoglobin is 6.7 volumes per cent unsaturated. As a result of certain modifying factors (p. 375)

³The presence of abnormal compounds of hemoglobin, e.g., methemoglobin and sulphohemoglobin, resulting from the action of various toxic substances, causes a type of cyanosis (enterogenous cyanosis), but these will not be considered here (see p. 44). Cyanosis may result from anoxia of either the anoxic or stagnant type. It obviously cannot occur in the anemic type, which is due essentially to a low hemoglobin concentration, in the histotoxic type in which the hemoglobin gives up less of its oxygen store than in health, nor in the anoxic and stagnant types if a severe grade of anemia exists.

the precise level of capillary unsaturation at which cyanosis makes its appearance varies in different cases between 6 and 7 volumes of oxygen per cent.

The oxygen unsaturation of the capillary blood does not of course occur abruptly at the arterial end but is progressive from point to point along the course of the vessel. The loss of oxygen may be uniform from the arterial to the venous end of the capillary as shown in Curve I, figure 169, or the desaturation may occur mainly toward the venous end (Curve II) when the capillary blood would approximate arterial blood in its content of reduced hemoglobin. Under other circumstances the greatest oxygen loss may occur toward the arterial end (Curve III) when the unsaturation of the capillary blood would approach that of venous blood. It is not possible to obtain data from which the true curve may be drawn. The simplest of these curves (Curve I) is assumed and the average unsaturation of the capillary blood is taken

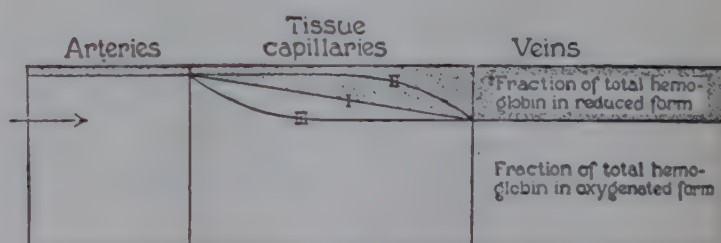


FIG. 169. Diagram showing hypothetical variations in the shape of the reduction curve of oxyhemoglobin during the passage of the blood through tissue capillaries. (After Lundsgaard and Van Slyke.)

as midway between that of arterial and venous bloods respectively. Thus

$$\frac{A + V}{2} = C$$

where A and V represent the unsaturation in volumes per cent of arterial and venous bloods respectively and C the mean unsaturation of the capillary blood.

For example, in a normal person the arterial unsaturation is 1 volume per cent (19 volumes per cent saturation), another 5 volumes per cent are given up in the capillary, the venous unsaturation is therefore 6 volumes per cent. So

$$\frac{1 + 6}{2} = 3.50 \text{ volumes per cent average unsaturation of capillary blood}$$

$$(3.5 \times 0.75 = 2.5 \text{ gram reduced Hb})$$

We have seen that the average unsaturation of the capillary blood must be between 6 and 7 volumes

per cent (approximately 5 grams of reduced Hb) before cyanosis appears. This degree of unsaturation of the capillary blood may be brought about either by an increase in the arterial unsaturation (anoxic type of anoxia) or as a result of a greater amount of oxygen being lost from the blood in its passage through the capillaries (stagnant type of anoxia). That is, by an increase in the venous unsaturation (V) alone. In order to produce an average unsaturation of from 6 to 7 volumes per cent in the capillary blood the arterial unsaturation would need to be from 4 to 4.5 volumes per cent, or the unsaturation of the venous blood—that in the arteries being normal—11 to 13 volumes per cent. Meakins and Davies found that when the veins of the arm were obstructed in normal individuals cyanosis was just detectable when the venous blood reached an unsaturation of 11.4 volumes per cent.

These facts may be clarified by examples. If the blood as it leaves the lungs contains only 15.5 volumes per cent of oxygen, i.e., if it has an unsaturation of 4.5 volumes per cent and the tissues abstract the usual quantity of oxygen, namely 5 volumes per cent, the unsaturation of the venous blood will be 9.5 volumes per cent and that of the capillary blood

$$\frac{4.5 + 9.5}{2} = 7 \text{ volumes per cent}$$

$$(7 \times 0.75 = 5.2 \text{ grams Hb}).$$

If on the other hand the arterial unsaturation is around the normal value of 1 volume per cent but as a result of slowing of the circulation each unit volume of the blood gives up a greater quantity of oxygen, and the venous unsaturation is increased to say 13 volumes per cent, the average unsaturation of the capillary blood will be

$$\frac{1 + 13}{2} = 7 \text{ volumes per cent}$$

In either of these instances slight cyanosis would be expected to appear.

Let us now consider what occurs when the hemoglobin percentage is above or below the normal value respectively.

In *anemia* the hemoglobin is below normal and the oxygen capacity of the blood is correspondingly lowered. If the hemoglobin content be only 30 per cent of the normal, the volumes per cent of oxygen in the arterial blood, though the latter be fully saturated, will be only about 6 volumes per cent, i.e., the quantity of hemoglobin in 100 cc.

of blood is less than 5 grams. It is obvious that such a person could not become cyanosed even if as a result of defective oxygenation of the blood or of slowing of the circulation, all his hemoglobin were in the reduced state. A patient whose hemoglobin was, say, 60 per cent (oxygen capacity 12 volumes per cent) would, like one with a normal hemoglobin content, become cyanosed when his arterial blood reached an unsaturation of about 4.5 volumes per cent, that is when his capillary blood had an average desaturation of around 7 volumes per cent. But the oxygen want of the anemic subject would be greater than that of the subject with a normal hemoglobin content since in the case of the former 4.5 volumes per cent constitute nearly 40 per cent of the oxygen capacity of his blood. In a less enlightened age when bleeding was resorted to for the relief of cyanosis, the brilliant success of that procedure is not to be wondered at—nor that the patient died. In the stagnant type of anoxia the unsaturation of the venous blood of a subject with 60 per cent hemoglobin content could not reach the value necessary to produce cyanosis until all the hemoglobin was in the reduced state. Thus $\frac{1 + 12}{2} = 6.5$ volumes per cent unsaturation of the capillary blood.

In *polycythemia*, in which the hemoglobin content is, say, double the normal (oxygen capacity 40 volumes per cent), cyanosis occurs in very mild degrees of anoxemia. At an arterial unsaturation of 4.5 volumes per cent the polycythemic subject would have the same degree of cyanosis as an ordinary person with this quantity (5 grams of reduced hemoglobin in his blood. But in the polycythemic subject with a hemoglobin content of 200 per cent, 4.5 volumes per cent is only 1 per cent of the oxygen capacity of his blood; in the person with a normal hemoglobin content it constitutes 22.5 per cent. The oxygen want in the former would be relatively slight as compared with that of the latter. Or put in another way and including the anemic subject—if the anoxemias were of the same degree in each, the anemic person would show little or no cyanosis; the polycythemic, a cyanosis of high degree and the normal subject a color intermediate in intensity. In a person with an abnormally high blood count a degree of slowing of the peripheral blood flow which would be without effect upon one possessing a normal hemoglobin content will result in cyanosis. Thus in regions such as the face, ear lobes and hands, where the cutaneous vessels are wide

filled with blood, cyanosis is readily induced in the polycythemic subject by exposure to cold. In certain conditions associated with arterial anoxemia, e.g., emphysema (p. 368) and congenital heart disease the red cell count is increased and the cyanosis, in consequence, enhanced.

The factors which influence the depth of cyanosis caused by a given quantity of reduced hemoglobin

(a) *The state of cutaneous capillaries.* When these are dilated more of the dark colored blood will be present in the skin than when they are constricted. In the former instance the cyanosis will of course be more pronounced. Increased carbon dioxide tension in the blood causes capillary dilatation, therefore, when retention of this gas accompanies oxygen want as in obstruction of the trachea, emphysema, venous congestion of superficial regions, etc. the cyanosis is intense. When, on the other hand, the carbon dioxide tension is low the cutaneous vessels are constricted. In the anoxemia resulting from rapid shallow breathing (p. 365) therefore the cyanosis tends to be of a pale leaden or heliotrope hue.

(b) *Pigmentation and thickness of the skin.* These factors obviously will modify the depth of the cyanotic color. Cyanosis is more clearly evident in regions where the skin is thin and unpigmented. The yellow discoloration of the skin caused by an excess of bilirubin in the blood (jaundice) tends to modify the cyanotic tint, but since the former stains the skin itself, while the discoloration due to reduced hemoglobin is confined to the capillary vessels, jaundice is likely to be just as intense in regions where the skin is thick as in those where it is thin. The cyanotic discoloration can be temporarily abolished by pressure upon the skin whereas the icteric staining cannot. Cyanosis does not appear in the conjunctivae but these are deeply colored in jaundice.

OXYGEN THERAPY

In combating certain forms of anoxia oxygen administration is a measure of the utmost value. The suitability of a given case for oxygen treatment is dependent upon certain quite definite principles which must be clearly understood. It is not to be expected that anoxia of the stagnant or anemic type would be materially benefited by such therapy since in these the arterial blood is already nearly fully saturated. The most that could result would be an increase in the quantity of oxygen held in simple solution and an unim-

portant rise in the oxygen saturation of the hemoglobin. Nor would anoxia due to a shunt of blood from the right to the left side of the heart (p. 371) or through a similarly completely unaerated portion of the lung be benefited by oxygen inhalations; it is not possible to make the blood supplying healthy and well aerated alveoli absorb any important amount of *extra* oxygen and so compensate for the shunted venous blood (p. 364).

When, however, the diffusion coefficient of oxygen (p. 314) through the alveolar membrane is reduced as a result of edema, thickening or a coating of fluid, oxygen administration by raising the pressure of the gas in the alveolar air will increase its rate of diffusion across the pulmonary epithelium. The oxygen saturation of the blood flowing through the damaged pulmonary tissue is increased.

Consequently, in broncho- or lobar pneumonia when such changes are responsible for the anoxemia, or in pulmonary edema whether from cardiac, pulmonary disease or gas poisoning, the success of oxygen administration is often spectacular. Anoxemia increases the permeability of the pulmonary epithelium to fluids and, consequently encourages edema formation. In other words, a vicious circle is established—edema inducing anoxemia and the latter increasing the edema—which is broken by oxygen administration. It is difficult for one to know the conditions which prevail in the lung in any given case before the treatment has been instituted. The relief of cyanosis, the lessening of restlessness or delirium and of the other signs of anoxemia in response to the treatment indicate that it is effective and, consequently, that the oxygen want is not due to a shunt of blood through channels inaccessible to a high pressure of oxygen.

Anoxemia due to rapid *shallow breathing* is relieved by oxygen treatment since the oxygen tension of poorly ventilated alveoli is raised thereby. The shallow breathing itself is likely to persist since it is primarily due to the local process in the lung acting upon the nerve endings rather than to the anoxemia. Therefore this type of breathing could, no more than the pulmonary lesion itself, be expected to be abolished by oxygen treatment. Nevertheless, since shallow breathing is aggravated by oxygen want it will be ameliorated by oxygen treatment—the vicious circle is broken. Yandell Henderson is a strong advocate for the use of carbon dioxide in combination with oxygen in such cases for the

purpose of deepening and slowing the respirations. That is, the chemical factor in respiratory control is employed to overcome the nervous element—the Hering-Breuer reflex. The prevention of acapnia also removes a hazard to the circulatory functions. Carbon dioxide inhalations alone constitute a valuable measure for the prevention of secondary pneumonias, e.g., post operative, and of pneumonia of the new-born. The high concentration of carbon dioxide in the inspired air favors full expansion of the lung and so circumvents bronchial occlusion and atelectasis.

Oxygen administration is also of definite value in congestive heart failure. This is so, even though anoxemia is absent or of very mild degree. The beneficial effect in such instances is difficult to explain; it is possible that the increased oxygen tension of the blood induced by the treatment exerts a direct specific effect upon the cardiac muscle.

Methods of oxygen administration

Pure oxygen or oxygen (93 per cent) and carbon dioxide (7 per cent) is supplied from a storage cylinder. The old method of administration, namely, the delivery of the gas by means of a funnel held in front of the patient's face and connected by tubing to the oxygen supply, is practically worthless; most of the gas is wasted. In modern methods the patient is placed in an air-tight chamber or the upper part of his body in an oxygen tent. The latter as compared with the former method is much less expensive, more convenient and just as effective (fig. 170). The concentration of oxygen in the atmosphere of the tent is raised to and maintained at from 40 to 60 per cent according to the features of the particular case. The administration should be con-

tinuous. It should be instituted early and before anoxemia due to cardiac involvement and the consequent slowing of the circulation has been added to the anoxemia caused by the pulmonary condition. It should be remembered that very high concentrations of oxygen are definitely toxic to animals and plants and that even concentrations of 70 or 80 per cent may be injurious to the pulmonary epithelium. When carbon dioxide is employed with oxygen its concentration in the tent air is maintained at around 4 or 5 per cent.*



FIG. 170. Photograph of the Barach-Davidson oxygen tent.

Helium (atomic weight 4, density $\frac{1}{7}$ that of nitrogen) is lighter than any other gas except hydrogen. Barach has applied this physical fact to reduce the respiratory effort in asthmatic attacks, in those suffering from laryngeal or tracheal obstruction and in certain other types of dyspnea. A gas mixture is used in which helium is substituted for nitrogen (oxygen 21 per cent, helium 79 per cent). For the relief of anoxemia the oxygen percentage may be increased to between 30 and 40 per cent.

* The patient's own breath adds from 1 to 2 per cent to the atmosphere of the tent.

SECTION IV. THE EXCRETION OF URINE

CHAPTER XXXVI

URINE FORMATION: THE STRUCTURE OF THE KIDNEY; THEORIES OF RENAL FUNCTION; VOLUME AND COMPOSITION OF THE URINE

THE STRUCTURE OF THE HUMAN KIDNEY

THE NEPHRON. This is the functional unit of the kidney. It comprises (1) the *renal (or Malpighian) corpuscle*, and (2) the *renal tubule*, which is divisible into (a) the proximal convoluted tubule, (b) the loop of Henle, and (c) the distal convoluted tubule. There are about 1 million nephrons in each human kidney (fig. 172).

(1) The **RENAL CORPUSCLE** consists of what appears to be a twisted skein of capillary channels—the *capillary tuft* or *glomerulus*—which in development has become invaginated into the upper blind end of the primitive renal tubule. The narrow, funnel-like cavity resulting from this invagination, and which almost completely surrounds the capillary tuft is known as *Bowman's capsule* (fig. 171). The capsular wall therefore consists of a *visceral* and a *parietal* layer. The former is a delicate membrane of flat cells. It envelopes each capillary loop and blends with the vascular wall. This layer becomes folded upon itself and continuous with the parietal layer at the point where the afferent and efferent vessels (see below) enter and leave the glomerulus. The cells of the parietal layer are for the most part squamous in type but become cuboidal near the point where the capsule empties into the tubule. The renal corpuscle measures about 200 microns in diameter. The total surface of the capillary loops of both kidneys is about 1.5 square meters. The renal corpuscles and the convoluted tubules lie in the cortex of the kidney. •

The **PROXIMAL CONVOLUTED TUBULE** is a tortuous tube (about 55 μ in diameter and 14 mm. long) lying in close relation to the renal corpuscle, and into which the latter empties. Its walls are composed of a single layer of cuboidal cells which differ from those lining other parts of the renal tubule in possessing delicate vertical striations at their free borders—the *brush or bristle border*. This appearance is suggestive of the striations seen in the epithelial cells lining the small intestine (Cowdry). The basal portions of the cells show a reticulum of protoplasmic threads radially arranged—the so-called *rods*. The length of the proximal tubule when uncoiled is some 15 mm. Its lumen varies in diameter from 15 to 25 microns in accordance with the quantity of fluid passing through it. The combined area of the 1,000,000 proximal tubules in a human kidney is nearly 1 square meter.

HENLE'S LOOP follows the proximal convoluted tubule and consists of a *descending* and an *ascending* limb, both of which lie for the most part within the renal medulla. The proximal two-thirds of the descending limb, though it follows a nearly straight or a moderately tortuous course, has about the same diameter as that of the proximal convoluted tubule and is lined by similar cells. The distal third of the descending limb becomes greatly narrowed and is lined by clear flat cells. The function of this part of Henle's loop is not definitely known, but it has been suggested that it serves to regulate the pressure of fluid within the tubule. Beyond the narrowed portion the tubule (ascending limb) widens again to its previous diameter. This portion is lined by cuboidal or columnar epithelium and is continued into the distal convoluted tubule. The average length of Henle's loop is about 16 mm.

The **DISTAL CONVOLUTED TUBULE** resembles the proximal convoluted tubule and lies coiled in close relation to the renal corpuscle. Its cells, however, have no brush border but resemble those forming the wide portion of the ascending limb of Henle's loop. Its length when uncoiled is about 5 mm. The distal tubule comes into contact over a limited area with the wall of the afferent vessel just before the latter enters the glomerulus. At this point the lining cells of the tubule assume a columnar shape; their nuclei are densely packed. The whole structure has a plaque-like appearance and is known as the *macula densa*, the term first applied to it by Zimmerman. This part of the afferent arteriole also undergoes a conspicuous structural change (p. 379). The distal convoluted tubule drains into the collecting duct system.

The length of a single nephron when straightened out is between 1½ and 2 inches, and a conservative estimate of the total length of the tubules of both kidneys from Bowman's capsule to the first collecting duct is some 45 miles. The total tubular surface cannot be far from 6 square meters.

A **SYSTEM OF COLLECTING TUBULES** conveys the urine to the kidney pelvis. These tubules are merely conduits and apparently possess no other function. The smallest of the collecting tubules (the *initial* or *connecting tubules*) receive urine from the distal convoluted tubules. Several connecting tubules from neighboring nephrons join to form a larger channel. Through a succession of such unions of smaller ducts and the creation of larger ones, relatively large short tubes—the *papillary ducts* (or *ducts of Bellini*)—are

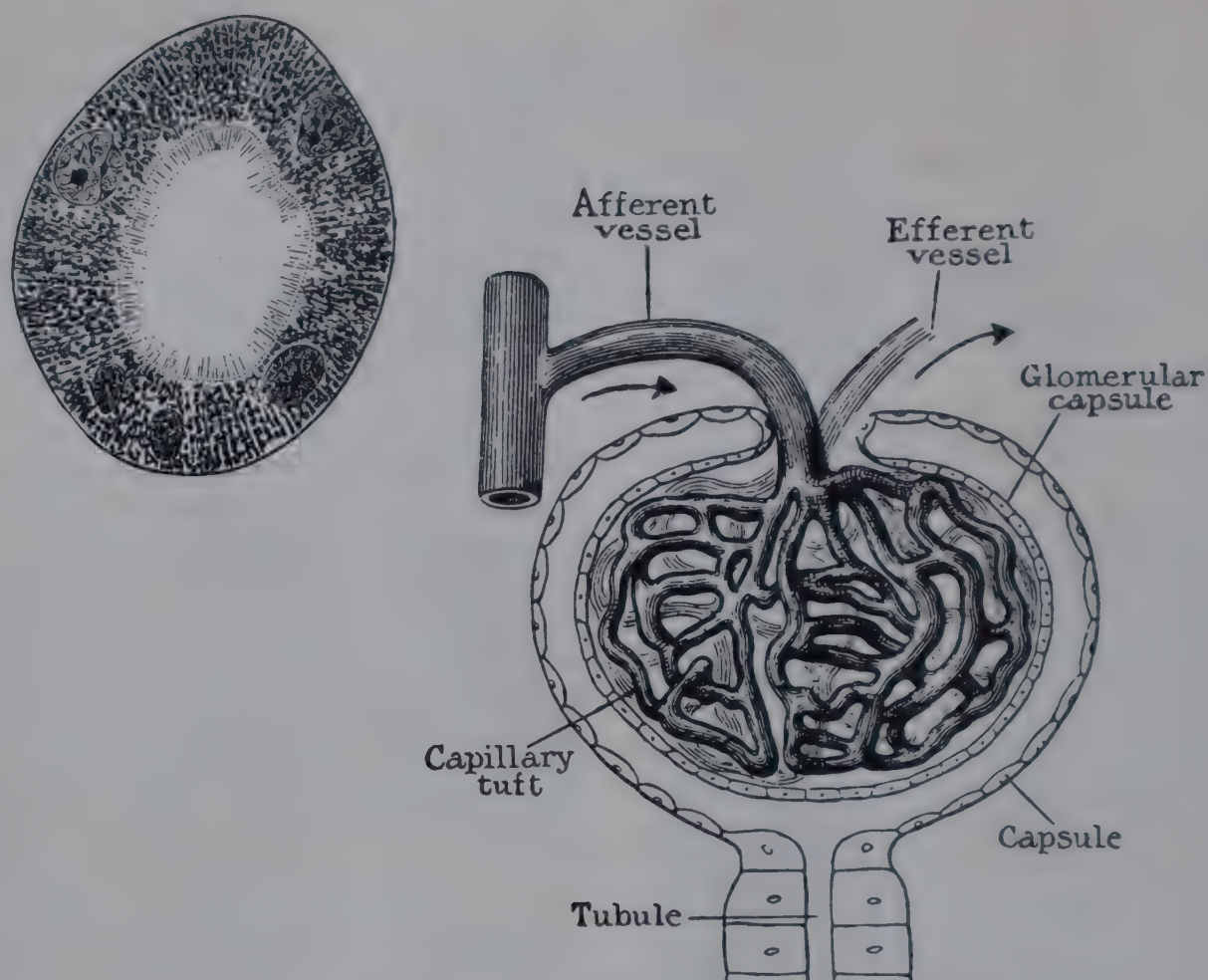


FIG. 171. Upper drawing, cross section through the convoluted tubule of a dog's kidney showing brush border (From Maximow and Bloom.) Lower drawing, diagram of Malpighian corpuscle. (After Cushny.)

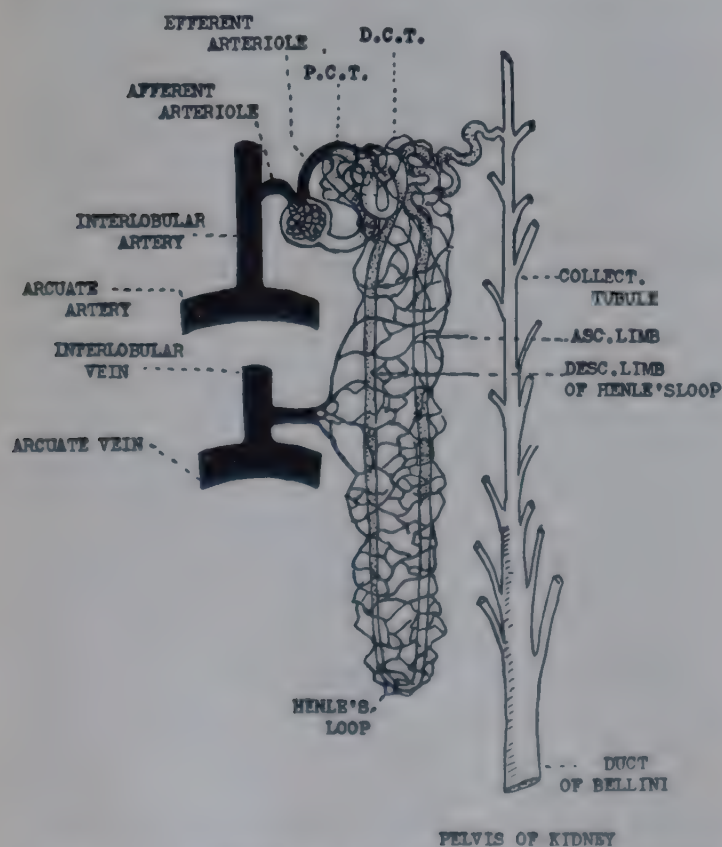


FIG. 172. Diagram of the tubules and blood supply of the kidney. P.C.T. = proximal convoluted tubule; D.C.T. = distal convoluted tubule.

finally formed which open into the renal pelvis at the apices of the papillae (fig. 172).

BLOOD SUPPLY. The renal artery upon entering the hilus of the kidney breaks up into numerous branches—

interlobar arteries—which pass outward between the renal pyramids to the junction of the cortex with the medulla. Here they turn to follow a more horizontal course and form arterial arches across the bases of the pyramids. From these vessels—called *arcuate arteries*—arise the *interlobular arteries* which run outwards through the cortex for variable distances and give origin to a series of small twigs. Each of the latter with few exceptions enters a renal corpuscle and constitutes the *afferent vessel* of the glomerulus. The afferent vessel throughout the greater part of its course has the features of an arteriole; it contains muscle fiber and has a diameter of about 50 microns. Upon entering the renal corpuscle and breaking up into a limited number of primary and secondary branches it gives rise to a leash of some 50 capillary loops which constitute the glomerular tuft. There is no anastomosis between any of these loops, and each is enveloped in a prolongation of the visceral layer of Bowman's capsule, much as the small intestine is covered by its serous coat, or as Vimtrup expresses it, "as a finger is covered by a glove." Nothing therefore separates the blood in each capillary from the cavity of Bowman's capsule except two delicate membranes which together have a thickness of about 1 micron. The capillary loops after a course of some 0.5 mm converge to form the *efferent vessel*, which leaves the renal corpuscle close to the point of entrance of the afferent vessel. The diameter of the efferent vessel is only about one-half that of the afferent; its section

area is therefore only about one-quarter that of the latter.

The wall of the afferent vessel just before it enters the glomerulus loses its elastic membrane, the endothelium becomes discontinuous and the muscle fibers are overlaid and in part replaced by a cushion of myo-epithelioid cells (the *polkissen* of Zimmerman). We have seen (p. 377) that the distal tubule comes into contact with this part of the afferent vessel. The efferent vessel near its origin also contains discrete groups of myo-epithelioid elements. Cells possibly of a neural or secretory character are also found in the angle between the afferent and efferent arterioles. (The myo-epithelioid cells in the walls of the glomerular arterioles, together with those just mentioned in the angle between them constitute what has been termed the "juxta-glomerular apparatus." This structure, which also contains numerous nerve fibers has been thought by some to serve, an endocrine function, namely, the regulation of the glomerular blood flow by the liberation of renin (p. 132). Its hypertrophy in hypertension has been reported. The macula densa of the distal tubule (p. 377) probably should be considered functionally as an integral part of such a mechanism.

The distribution of the efferent vessel varies in accordance with the level in the kidney at which it arises;—(a) those which leave glomeruli situated in the outer part of the cortex break up into a network of capillaries which supply the proximal and distal convoluted tubules of this region. The efferent vessel from a given glomerulus as a rule supplies only the convoluted tubule of that nephron, i.e., there is little or no anastomosis between the circulations of neighboring convoluted tubules. (b) Those arising in the boundary zone between cortex and medulla soon divide into a leash of straight wide vessels—*arteriae rectae*—which run toward the kidney pelvis between the tubules of the medulla—Henle's loop and collecting tubules—around which they form a capillary network. (c) Those which combine the features of (a) and (b). These are found in the deep portions of the cortex. They first break up into branches for the supply of the convoluted tubules and then form straight vessels for distribution to the tubules of the medulla.¹

THE VENOUS RETURN. The blood having traversed the capillary vessels surrounding the convoluted tubules is collected into a venous plexus in the cortex. The blood from this plexus passes successively through interlobular, arcuate and interlobar veins which accompany the corresponding arteries. The interlobar

¹ Some of the afferent arterioles give off a communicating vessel (Ludwig's arteriole) which by-passes the glomerulus and connects with the capillary plexus surrounding the tubules. Occasionally an interlobular artery also gives off a branch which joins the capillary plexus directly. The number of these extra-glomerular vessels and consequently their functional importance is a matter of dispute. They increase in size in chronic kidney disease and then probably play a more important rôle than in health.

veins become confluent near the hilus of the kidney to form the renal vein. The capillary network derived from the *arteriae rectae* drain into *venae rectae* which in turn empty into the interlobular veins.

There are certain anatomical features of the renal circulation of special physiological interest which should be emphasized.

(1) Nearly all the blood which enters the kidney passes through the glomerular tufts.

(2) The tubules are therefore supplied largely by blood which has first passed through the glomeruli.

(3) The renal artery breaks up quite suddenly into short branches. This fact, to which attention was first drawn by Bowman, ensures that blood is delivered to the glomerular vessels under a high head of pressure. It should also be remembered that the renal artery is short, arises directly from the aorta, and is very large proportionately to the mass of tissue which it supplies.

(4) There is a striking disparity between the diameters of the *afferent* and *efferent* vessels.

The renal nerves

The kidney receives a sympathetic and a parasympathetic innervation.

(1) The SYMPATHETIC FIBERS arise from the sixth thoracic segment to the third lumbar inclusive. Functionally the fibers are of two types, *vasoconstrictor* and *afferent*. They are conveyed to the kidney in the *greater, lesser* and *least splanchnic nerves*. The greater and lesser splanchnic fibers synapse in the semilunar ganglion. The postganglionic fibers upon leaving the ganglion enter into the formation of the *renal plexus*, into which are also interlaced fibers of the vagus. From this plexus, which surrounds the renal vessels, non-medullated fibers may be traced to the arterioles, and to the glomerular and tubular capillaries. Nerve filaments have even been described between the cells of the tubules and of Bowman's capsule. The presence of ganglion cells within the substance of the kidney is a disputed question. The fibers of the least or lowest splanchnic nerve connect with cells within the renal ganglion situated in the hilus of the kidney; postganglionic fibers enter the renal substance.

(2) The PARASYMPATHETIC FIBERS are derived from the vagus. Their functions are unknown. The evidence is against either this nerve or the sympathetic supplying true secretory fibers to the renal cells. The effects upon urine formation caused by section or by the stimulation of any of the renal nerves are believed to be entirely the result of the vascular change which such section or stimulation has brought about. Carrel and Guthrie, and Quinby excised the kidney and transplanted it into another position. Though completely denervated by this procedure, the kidney excreted urine of the usual composition.

THEORIES OF RENAL FUNCTION

Bowman (1842) discovered the fundamental fact that the capsules surrounding the glomerular tufts are simply the expanded extremities of the renal tubules. Struck by the design of the glomerulus, which seemed to fit it so admirably to the purposes of a filter, he believed that this structure filtered water but that the solids of the urine were *secreted* by the cells of the tubules. Heidenhain maintained that the formation of urine was entirely a secretory process. Water and salts were the products of the glomerular membrane, while the more characteristic urinary constituents, urea, uric acid, etc., and under certain conditions water as well, were secreted by the tubular epithelium (see p. 386). He and his followers have endeav-

only be the same as those of plasma (less the proteins) but, if water alone underwent reabsorption, they should all be concentrated in the urine to precisely the same degree. We know that this is not so. Urea, for instance, is concentrated some 60 times, creatinine 70 times or more, whereas chloride may be concentrated only twice, and sugar appears in the urine in traces, if at all (see table 30). Either simple filtration must be deleted from Ludwig's theory and selective secretion substituted, or the conception of the reabsorption of water alone must be replaced by one postulating the re-absorption of water and certain solids in different relative proportions. Cushny's theory retains simple filtration by the glomerulus but postulates such a *selective re-absorption* by

TABLE 30

Showing composition of plasma, glomerular filtrate, reabsorbed fluid and urine (modified from Cushny)

	90 LITERS PLASMA CONTAIN		83 LITERS FILTRATE CONTAIN	82 LITERS REABSORBED FLUID CONTAIN		1 LITER URINE CONTAINS	
	Per cent	Total		Per cent	Total	Per cent	Total
Water	92	83 liters	83 liters		82 liters	95	950 cc.
Colloids.....	7.5	6750 gr.					
Glucose.....	0.1	90 gr.	90 gr.	0.11	90 gr.		
Sodium	0.3	270 gr.	270 gr.	0.32	266.5 gr.	0.35	3.5 gr.
Chloride	0.37	333 gr.	333 gr.	0.4	327 gr.	0.6	6.0 gr.
Urea	0.03	27 gr.	27 gr.	0.008	7 gr.	2.0	20.0 gr.
Uric acid.....	0.004	3.6 gr.	3.6 gr.	0.003	3.1 gr.	0.05	0.5 gr.
Potassium.....	0.02	18.0 gr.	18.0 gr.	0.02	16.5 gr.	0.15	1.5 gr.
Phosphate.....	0.009	8.1 gr.	8.1 gr.	0.0008	6.6 gr.	0.15	1.5 gr.
Sulphate	0.002	1.8 gr.	1.8 gr.			0.18	1.8 gr.
Creatinine	0.001	0.7 gr.	0.7 gr.			0.07	0.7 gr.

ored by almost countless experiments—largely involving the injection of dyes and the demonstration that these appeared in high concentration in the tubule cells—to prove the secretory function of the tubules. The theory of Ludwig was based upon purely physical conceptions. He believed that the glomerulus acted as a filter to remove from the plasma, water and all substances other than the proteins; and that the filtrate was concentrated in the tubular lumen through the return of the greater part of the water to the blood, by means of a simple process of diffusion.

Cushny's "Modern theory"

It is quite obvious that Ludwig's theory cannot be correct in its entirety; if filtration be granted, then the several urinary solids should not

the tubules. According to this theory the reabsorbed fluid is of constant composition under a conditions of health and resembles Locke's solution, i.e., one containing sodium, calcium, potassium, magnesium, chlorine and sugar, and in addition, small quantities of urea, uric acid, and phosphate. A selective process of this nature cannot be explained upon the basis of known physical laws, but entails "vital" activity, i.e. the performance of work by the tubular epithelium. Filtration, on the other hand, is "due to blind physical force." The glomerular membrane plays a passive rôle, performing no work (see table 30). These two processes, glomerular filtration and tubular re-absorption will now be considered in detail.

EVIDENCE FOR GLOMERULAR FILTRATION

(1) **STRUCTURE.** The peculiar features of the renal circulation—the great number of capillary loops in the glomerular tuft, the disparity between the calibres of its afferent and efferent vessels, the origin of the renal artery directly from the aorta, and its abrupt division into branches (p. 378) indicate that the development of pressure within the tuft is an important requirement for urine formation, and consequently strongly suggest that this part of the renal unit acts simply as a filter. On the other hand, a close examination of the glomerulus reveals nothing which might suggest its performing a secretory function.

(2) **THE FILTRATION PRESSURE.** [In order to drive fluid through a permeable membrane, there must be a higher pressure on one side. Variations in this pressure will alter the volume but not the composition of the filtrate. If urine formation involves filtration, alterations in the glomerular pressure should cause corresponding changes in urine volume. The glomerular pressure, however, depends not only upon the difference between the blood pressure within the capillary loops and the pressure in Bowman's capsule, but also upon the osmotic pressure of the colloids (proteins) of the plasma. This colloid pressure, which amounts to between 25 and 30 mm. Hg, opposes the pressure of the blood within the glomerular tuft. In other words, such an osmotic pressure requires that, in order for filtration to occur, the blood pressure shall be 25 or 30 mm. higher than it would need to be were the plasma protein-free.] The *effective* filtration pressure, or actual driving force, may be expressed thus—

$$P_b^{(75)} - P_o^{(30)} - P_c^{(5)} = P_f^{(40)}$$

Where P_b = blood pressure, P_o = osmotic pressure of proteins, P_c = pressure in Bowman's capsule and P_f = effective filtration pressure (see fig. 173).

Hayman measured the pressure in the afferent arterioles and the capillaries of the frog's kidney simultaneously with the aortic pressure. The method employed in measuring the pressure in the renal vessels was one based upon the general principle employed in human blood pressure estimations. A fine pipette was inserted into Bowman's capsule and the proximal convoluted tubule occluded by compression with a glass rod. Fluid was then run into the capsule under measured pressures. The pressure at which blood was observed to enter the vessels of the tuft, during systole only, was taken as the index of the systolic

pressure in the afferent vessel. As the pressure was gradually lowered below this level the flow in the capillaries became continuous. The pressure at which this occurred was taken to correspond to the pressure (diastolic) in the capillary loops. The following mean values were obtained.

Systolic pressure in aorta..	37.4 cm. H ₂ O
Systolic pressure in afferent vessel.....	31.6 cm. H ₂ O
Diastolic pressure in capillaries.....	20.2 cm. H ₂ O, or 54 per cent of the systolic aortic pressure

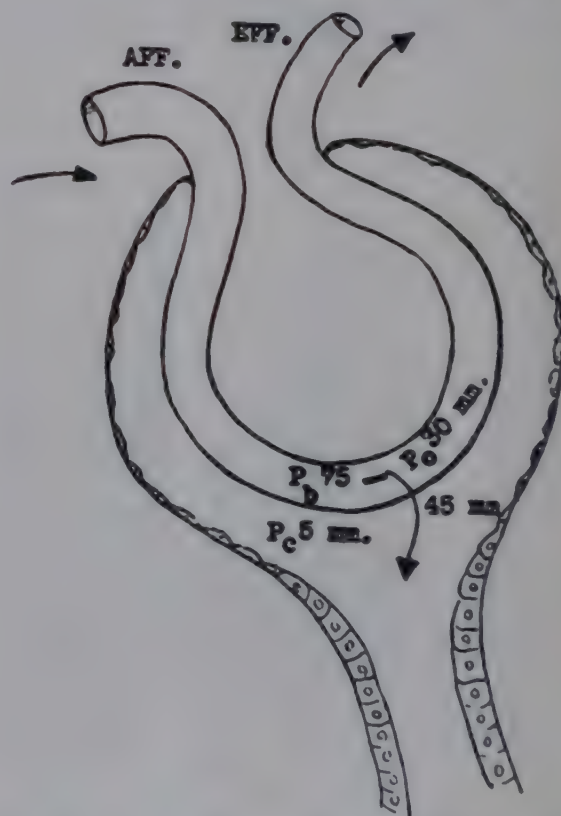


FIG. 173. Diagram illustrating the relation of blood pressure (P_b), osmotic pressure (P_o) and capsular pressure (P_c) upon the formation of urine. Aff. = afferent arteriole, Eff. = efferent arteriole.

Capillary pressures as high as 70 per cent of the aortic pressure were observed.

Numerous experiments of various types have been carried out to investigate the effects of one or other of the three factors mentioned above (P_b , P_o and P_c) upon the formation of urine. In general the results accord with a filtration process.

(a) *Blood pressure.* [Raising the general blood pressure causes a corresponding change in the urinary flow, provided that the agent which raises the systemic pressure does not cause a reverse change in the blood pressure within the kidney itself.] Stimulation of the splanchnic nerves, for example, with the renal nerves intact is likely to result in a reduction in urine volume from the kidney of that side, since its vessels share in the general vasoconstriction and the glomerular pressure is reduced. If the renal nerves are first cut, how-

ever, the general vasoconstriction and the renal vasodilatation (removal of constrictor tone) caused a higher pressure within the vessels of the kidney and a profuse flow of urine. Division of the cord in the thoracic region, by reducing the general blood pressure through the removal of vasoconstrictor tone, reduces the urinary flow. The fall in blood pressure following hemorrhage acts similarly.

(The rate of the renal blood flow as well as the pressure within the glomerulus, will be altered by the foregoing measures, and the altered blood flow, rather than the change in blood pressure, might be held responsible for the greater urine production. It was shown, however, by Richards and his associates that variations in glomerular pressure by itself caused parallel changes in urinary flow when special means were employed to

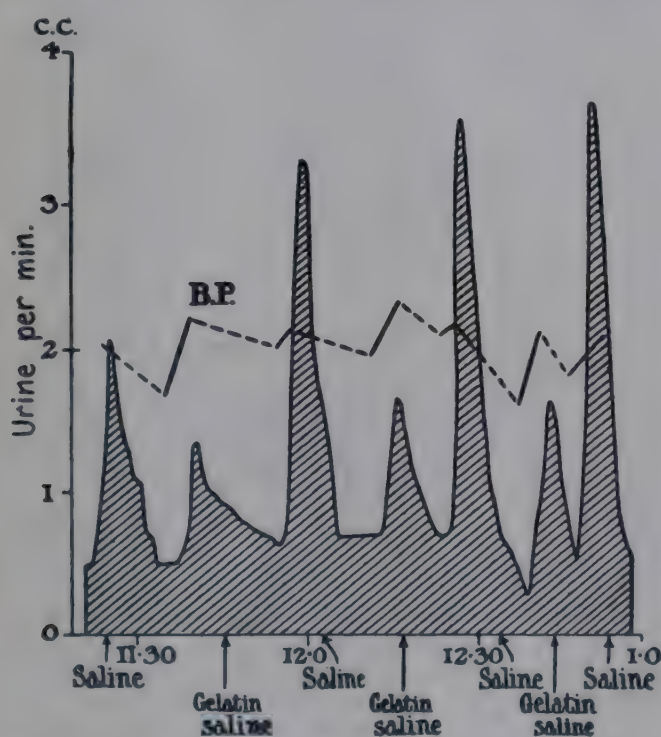


FIG. 174. Illustrating the effect of the intravenous injection of saline and of a gelatine-saline solution, respectively, upon the flow of urine. B.P. = blood pressure. The figures along the abscissa indicate the time in half-hours. (After Knowlton.)

keep the renal blood flow constant. It was also shown by these observers that in certain dosage adrenaline causes a relatively greater constriction of the efferent than of the afferent vessel. A rise in glomerular pressure and an increased flow of urine resulted.

(b) *Osmotic pressure of proteins.* As already stated, this amounts to between 25 and 30 mm. Hg. (The blood pressure in the capillaries of the tuft must therefore exceed the osmotic pressure in order that filtration shall occur (see also p. 43). The blood pressure in the capillary loop is around 60 per cent of the systolic aortic pressure, or from 70 to 80 mm. Hg. So then, over and above the sum of osmotic and intracapsular pressures, there exists a capillary pressure of from 35 to 50 mm. Hg which serves to drive fluid across the glomerular membrane. Reduction of the blood pressure by this amount (from 35 to 50 mm. Hg) suppresses urine formation.

The intravenous injection of isotonic salt solution causes profuse diuresis, resulting from, in part at least, the dilution of the plasma proteins; saline whose osmotic pressure has been raised by the addition of gelatin or gum acacia causes a diuresis only about one-third as great (fig. 174). Dilution of the plasma colloids permits the blood pressure to be reduced to a much lower level (under 20 mm.) before urine formation ceases. It is also well known that the urine volume is less in the standing position than in recumbency; this is due chiefly to the concentration of plasma protein which occurs in the former position (p. 20).

(c) *Intracapsular pressure.* Under ordinary circumstances this is low, probably not more than from 5 to 10 mm. Hg. It is largely due to the pressure of the surrounding renal substance (intrarenal pressure), for the kidney, it will be recalled, is enclosed in an inelastic fibrous capsule. When a manometer is tied into the ureter, the pressure in the tubules and capsule gradually rises. Urine formation ceases when the instrument registers a pressure equal to that by which the glomerular blood pressure exceeds the colloid osmotic pressure, i.e., when $P_o(30 \text{ mm.}) + P_c(45 \text{ mm.}) = P_b(75 \text{ mm.})$. Dilution of the proteins will permit the ureter pressure to be raised higher before urine formation ceases. The effect of raising the ureter pressure in suppressing urine formation is, of course, strong evidence for filtration; a true secretory process is not dependent upon a difference between the pressure in the vessels and that in the secretory ducts. The salivary gland, for example, continues to secrete though the duct pressure greatly exceeds the capillary blood pressure.

(3) *COMPOSITION OF THE CAPSULAR FLUID.* Wearn and Richards observed the glomeruli of the frog's kidney beneath the microscope and drew off fluid from Bowman's capsule by means of a fine pipette (fig. 175). The fluid had the composition of protein-free plasma. It was alkaline in reaction and contained urea, sodium chloride and glucose in practically the same concentrations as in plasma. Dyes injected into the animal appeared in the capsular fluid in the same concentration as in protein-free plasma. The molecular concentration and electrical conductivity of the capsular fluid and of de-proteinized plasma were also the same. The capsular fluid is therefore a filtrate. Walker and his associates have succeeded in recovering samples of fluid for analysis from the capsule and tubules of the mammalian kidney (guinea-pig and rat). The observations of Wearn and Richards upon the amphibian nephron have in general been confirmed.

(4) *THE PLASMA PROTEINS* when they pass into the urine do so in amounts which are inversely related to their molecular weights, showing that secretion plays no part, but that molecules escape through "pores" in the glomerular membrane. In kidney disease, serum albumin, which has a molecular weight of around 70,000, appears in the urine, as a rule, in greater amounts than does serum globulin (molecular weight

about 165,000).² Fibrinogen with a still larger molecule rarely escapes across the glomerular barrier. Hemoglobin, which has a molecular weight of a little over 68,000, when free in the plasma passes in the urine fairly rapidly,³ whereas hemocyanin, which has a huge molecule (mol. wt. 5,000,000) is not excreted. Inulins (mol. wt. 5200) and certain foreign proteins, such as egg white and gelatin with molecular weights around 35,000, and the abnormal Bence-Jones protein (p. 406) with a molecule of about the same size as the former two proteins are freely excreted. Edestin and casein, whose molecular weights are over 100,000, do not pass into the urine. The "pores" of the glomerular mem-

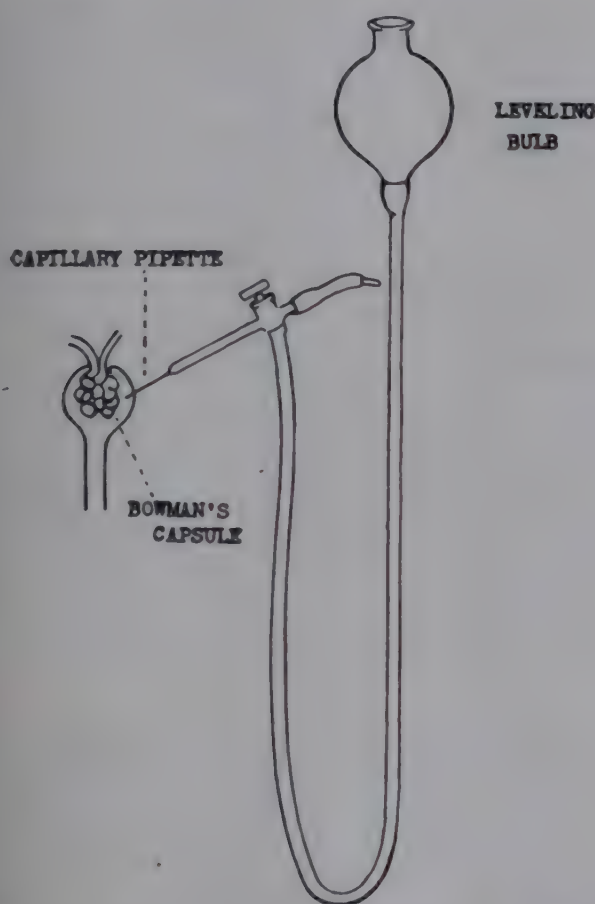


FIG. 175. Diagram showing Wearn and Richards method of obtaining a sample of fluid from Bowman's capsule. A fine glass rod (not shown in figure) is used to compress the proximal tubule just below the capsule and so to prevent fluid from being drawn from the tubule. When the glass bulb and tubing containing mercury is lowered, capsular fluid alone is withdrawn.

brane appear, therefore, to be of such a size as to allow the passage of molecules of a weight less than about

² Osmotic pressure determination.

³ Monke and Yuile estimate that only about 3 per cent of the "pores" of the glomerular membrane are sufficiently large to allow the passage of the hemoglobin molecule. It is possible, however, that the relatively free excretion of hemoglobin depends upon the fact that a proportion of the molecules are of smaller size than 68,000, that is, molecules with one, two or three atoms of iron, rather than that this small proportion of the "pores" are of such a size as to permit the passage of the largest molecules. These investigators find that part of the hemoglobin filtered through the glomerulus is reabsorbed from the tubules by phagocytosis.

70,000 (see Bayliss and associates and Bott and Richards). Hemoglobin and serum albumin are, therefore, near the border line, the former appearing in the urine only when its concentration in the plasma rises above 100 mgm. per 100 cc. Serum albumin may escape into the urine as a result, apparently, of even a slight change in the permeability of the glomerular membrane as in functional albuminuria (p. 405).

(5) OXYGEN CONSUMPTION. Certain measures, such as the injection of saline or the elevation of blood pressure, cause profuse diuresis but little or no increase in oxygen consumption (fig. 176). This is further evidence that physical processes are concerned, rather than secretion; the latter, of course, would entail oxidative processes and the expenditure of energy. Van Slyke and associates found that the oxygen consumption of the dog's kidney varied widely—from 0.04 to 0.30 cc.

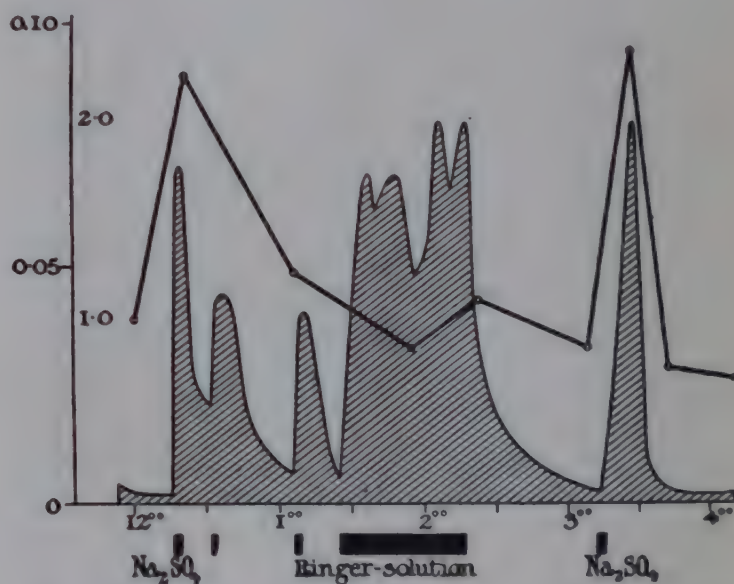


FIG. 176. Graph of oxygen consumption by the kidney during diuresis following the intravenous injection of Ringer's solution and sodium sulphate. The black line represents the oxygen in c.c. taken up by each gram of kidney per minute. The shaded areas denote the volume of urine secreted each minute. Time in half-hours. A marked rise in oxygen consumption results from sodium sulphate but not from Ringer's solution. (After Barcroft and Straub.)

per gram of renal tissue per minute—but no relation between the oxygen consumption and the quantity of water or urea excreted was observed.⁴

It has been calculated that only about 1 per cent of the oxygen consumed by the kidney is used in providing energy for its excretory function (reabsorption). The remainder is used in non-excretory processes. It may also be mentioned incidentally here that the blood in the renal vein is usually more than 85 per cent saturated with oxygen, indicating that the oxygen tension is maintained at a higher level in the renal tissue than in most other tissues.

⁴ The experiments were made upon unanesthetized animals; one kidney was removed; the other, upon which the observations were made, was transplanted to a subcutaneous position.

The evidence in the foregoing paragraphs is conclusive for the view that the mammalian glomerulus acts as a filter.

THE EVIDENCE FOR TUBULAR REABSORPTION

Since glomerular filtration is an established fact, some measure, at least, of reabsorption by the tubules must be admitted. This is self-evident, inasmuch as bladder urine contains less water, no sugar and usually less chloride than the glomerular filtrate does. Wearn and Richards found chloride and glucose absent from frogs' urine, yet these substances were present in the capsular fluid. Also, the volume of the urine was only about $\frac{1}{10}$ to $\frac{1}{20}$ of the calculated volume of the filtrate. Water, chloride and sugar quite evidently were reabsorbed from the filtrate during its passage along the tubules. (Those substances, such as glucose, amino-acids, vitamin C, chlorine, sodium, potassium and calcium, which are absorbed with water to a relatively large extent and consequently are absent from the urine, or in low concentration, are called *high threshold substances*.) High threshold substances, however, appear in the urine in greater amounts if their concentrations in the plasma rise beyond a certain optimal threshold. The glycosuria in diabetes and the hypercalcuria of parathyroid excess (p. 708) are examples. *Low threshold substances* are those which are highly concentrated in the urine, since they are reabsorbed in relatively small amounts or not at all. *Urea, uric acid, phosphates and sulphates* are reabsorbed in variable amounts. *Creatinine* is concentrated to a greater extent than any other urinary constituent since it is not reabsorbed (see table 30). In certain pathological states of the kidney, creatinine may undergo passive reabsorption.

As further evidence for reabsorption the following experiments may be mentioned. Cushny found that when the ureter of one kidney was partially obstructed and the flow along the tubules thereby delayed, the urine from the obstructed side was more concentrated but contained less total chloride than that from the opposite kidney. These changes can be accounted for only by a greater reabsorption of salt and water. Diuretics, by increasing the flow, caused the production of a more dilute urine but increased the total urinary chloride and urea. The more rapid flow along the tubules reduces the time during which the absorption of water and reabsorbable solids can occur. Bieter and Hirschfelder injected dye into frogs and observed the kidneys by Richards'

method (p. 832). The glomerular fluid was stained within 20 minutes. Concentration (reabsorption of water) occurred progressively along the tubule, the color being deepest in the distal convoluted tubule. After the tubules have been poisoned by mercury or cyanide, concentration does not occur. Poisoning of the tubule, however, though it abolishes the specific reabsorptive process permits water and other substances to pass back into the blood by a simple process of diffusion (see passive reabsorption). This latter process has been clearly demonstrated by Richards, who found that complete suppression of urine formation (anuria) may follow the administration of a tubular poison though filtration continues at the normal rate.

(The proximal tubule is responsible for the reabsorption of sugar, phosphate, sodium and part of the chloride, and for about 65 per cent of the water of the filtrate. The filtrate remains isotonic with the plasma in the proximal tubule. The remainder of the reabsorbed water and chloride is taken up by the distal part of the nephron. Here the filtrate becomes hypotonic and is acidified as a result of reabsorption of base.) Hemoglobin, when injected into the circulation, is deposited as the insoluble acid hematin when acted upon by the acid urine; this has been observed to take place in the distal tubule of the frog's kidney.⁴⁰

(In its transfer across the tubular membrane, phosphorylation of the glucose⁴¹ molecule appears to be a necessary preliminary step. The change is brought about by a specific enzyme, *kidney phosphorylase*. Dephosphorylation of the hexose phosphate thus formed is effected by a second enzyme, "*alkaline*" *phosphatase*, present in the cells of the proximal convoluted tubules.)

(The absorption of sodium from the proximal tubule is influenced by the adrenal cortex and the

⁴⁰ This fact has a practical bearing when large amounts of hemoglobin are liberated, as may occur after the transfusion of incompatible blood (p. 35).

⁴¹ Phloridzin acts selectively upon the proximal tubule preventing the reabsorption of glucose and the secretion of creatinine. The first of these effects is the cause of the "diabetes" following the administration of the drug. Phloridzin exerts this action most probably by inhibiting phosphorylase (Kalcar; Kritzler and Gutman), but has no effect upon the "*alkaline*" *phosphatase*. Lundsgaard suggested that phloridzin inhibited phosphorylation and dephosphorylation by *phosphatase*, but several observations have since been recorded which are opposed to this idea. Hudson and Walker, for example, found that iodoacetate which prevents the esterification of glucose by *phosphatase* did not cause glycosuria, nor is the *phosphatase* activity of the kidney abolished by phloridzin.

principle of the posterior pituitary gland. The hormone of the adrenal cortex is essential for the normal reabsorption of sodium; in adrenal insufficiency increased excretion of this element is, therefore an outstanding feature. The effect of corticosterone and of desoxycorticosterone is even more pronounced than that of cortin. The antidiuretic hormone of the pituitary, inhibits the reabsorption of sodium and chloride and increases the reabsorption of water.) According to Shannon, the (pituitary hormone acts upon the distal tubule in respect to the reabsorption of water and inhibits the reabsorption of sodium though an action upon the proximal part of the nephron. There is evidence that the parathyroid hormone lowers the renal threshold for phosphate. Thyroxine appears to antagonize the antidiuretic action of the pituitary hormone.)

Experimental evidence points to the cells of the distal part of the nephron as the site of the formation of ammonia and hippuric acid.

Smith and his associates find by means of the inulin clearance method (p. 404) that the quantity of filtrate formed by the human kidney is around 125 cc. per minute. At this rate nearly 200 liters of fluid would be filtered in 24 hours. Of this, about 99 per cent is reabsorbed by the tubules.

CRITICISMS AND MODIFICATIONS OF CUSHNY'S THEORY

In its broad outlines the filtration-reabsorption conception of renal function is firmly established on a sound experimental and clinical basis. Certain of its details however require revision in the light of certain experimental and clinical observations. The main modifications in Cushny's theory which more recent work has made necessary are concerned with the contention that the reabsorbed fluid is constant in its composition and the denial of tubular excretion. These questions will now be considered.

Constancy in composition of the fluid removed from the filtrate by reabsorption implies that under changing conditions of urinary flow the concentrations of the several low threshold substances should also remain constant, relatively to one another. Let it be supposed, for example, that 100 cc. of filtrate contains 20 mg. of urea and 1 mg. of creatinine and, after the reabsorption of water (together with sugar, salts and urea), 100 cc. of urine contain 1000 mg. of urea and 75 mg. of creatinine. The concentration ratio of urea ($\frac{\text{mg. urea in 100 cc. urine}}{\text{mg. urea in 100 cc. plasma}}$), therefore, is 50 and

that of creatinine 75. A reduction in the quantity of filtrate and, therefore, in the flow along the tubules will cause more fluid to be reabsorbed; if the composition of the reabsorbed fluid remained the same, parallel rises in the concentration ratios of urea and creatinine should occur. Such a relationship, however, does not hold, either in health or in disease. In brief, creatinine is not reabsorbed⁶ whether the urine flow is slow or rapid whereas the quantity of urea excreted in the urine varies, more being returned to the blood in the reabsorbed fluid with slow than with rapid rates of urine flow. The same is true of other constituents (e.g., uric acid and phosphates) of the glomerular filtrate.

(The constituents of the glomerular filtrate are grouped by Rehberg into three classes according to the manner in which they behave towards the reabsorption process: (a) Substances which are *actively reabsorbed*, namely, those already referred to on page 384 as high threshold substances (glucose, Na, K, Ca, Mg and Cl). These substances are conserved to the body and are usually in lower concentration in the urine and in higher concentration in the reabsorbed fluid than in the plasma. (b) Substances which pass back through the tubular epithelium by a simple process of *diffusion* when their concentrations in the tubular fluid rises above their concentrations in the plasma. These are the substances already referred to as low threshold substances, namely, urea, uric acid, endogenous sulphate and phosphates. They are *passively*, never actively, reabsorbed. It has been estimated that in health from 40 to 50 per cent of the filtered urea is returned in this way to the blood. These materials are never in lower concentration in the urine nor in higher concentration in the reabsorbed fluid than in the plasma. (c) *Non-threshold substances*, which suffer neither active reabsorption nor back diffusion. They are therefore absent from the reabsorbed fluid.

Rapid flow of urine along the tubules will reduce active reabsorption as well as back diffusion, but not both processes to the same extent. It is obvious that the more a substance undergoes active reabsorption or back diffusion, the less of it will appear in the urine. Back diffusion of low threshold substances and also apparently of a high threshold substance, such as chloride, is encouraged by a rise in their concentrations in the filtrate.) Experiments by Rehberg upon chloride

⁶ In kidney disease a considerable quantity of creatinine may be reabsorbed as a result of simple diffusion.

elimination showed that only when the chloride of the plasma was below 375 mg. chlorine per 100 cc. did the chloride concentration of the reabsorbed fluid⁷ exceed that of the plasma and of the urine (i.e., undergo active reabsorption). When the chloride concentration in the plasma was high (above 375 mg. chlorine per 100 cc.) its concentration in the reabsorbed fluid was always below that of the plasma and the quantity excreted in the urine was raised; in short, it was treated as a low threshold substance, passing into the reabsorbed fluid by back diffusion alone. Other high threshold substances probably behave in a similar way.

The question of excretion by the tubular epithelium

From Heidenhain's time to the present innumerable experiments have been performed in attempts to prove or disprove the secretory hypothesis. Only a few of the more important and more recent experimental results can be given.

(a) Marshall and Vickers found that injected phenol-red appeared in the plasma in two forms, of which one was *protein-bound* (unfilterable) and the other *free* (filterable). Following injection more dye appeared in the urine than the quantity of blood which was calculated to have passed through the kidney during the experiment could have contained in filterable form. Part of the dye, it was argued, must therefore have been excreted by the tubules. Also, when the blood pressure was reduced to the point where glomerular filtration ceased and the dye then injected, the kidney contained a higher concentration of dye than the serum or other tissues. Microscopical examination showed deposition of the dye in the cells of the convoluted tubules; it was absent from the lumen. The dye therefore entered the cells from the blood and not simply by re-absorption from the tubules. Sheehan has carried out cognate experiments and arrived at a similar conclusion concerning tubular function.

(b) Chambers and his associates have demonstrated the excretion of phenol red by the mesonephric tubule of the embryonic chick and by the metanephric tubule of a 3½ months human embryo. Employing a micro-manipulative technique the tubules were broken up into sections. Within the first few hours or so of incubation the open ends of the fragmented tubules close and their lumina then become distended with fluid transferred from the surrounding culture medium.

⁷ The reader is referred to Rehberg's papers for the details of the method for determining the composition of the reabsorbed fluid. Rehberg determined the filtration rate in human subjects from the creatinine clearance, believing that the substance was neither excreted nor reabsorbed. This has been shown to be erroneous; his filtration values were therefore too high. His general conclusions are, nevertheless, essentially correct.

Phenol red added to the culture medium was taken up by the tubular cells and concentrated within the cyst-like structures. Cooling the culture to 30°C. CO₂, H₂S or lack of O₂ stops the process, the tubular epithelium being then permeable in both directions to water and dye.

(c) Evidence for the tubular excretion of creatinine in man has been obtained by comparing its clearance with that of inulin (p. 404). Inulin is neither reabsorbed nor excreted by the tubules. Its clearance, which is therefore a measure of glomerular filtration is considerably lower than that of ingested creatinine. The latter must therefore be excreted by the tubules.

(d) The kidneys of certain fish (e.g. toad-fish) possess no glomeruli. Each nephron consists of a segment analogous to the proximal convoluted tubule of mammals. Nevertheless, urea, creatinine, phenol-red and such iodine compounds as diodrast and hippuran, when injected appear in relatively large amounts in the urine. Also, as shown by Marshall, the glomerular function of the sculpin can be abolished by phloridzin. The functionally aglomerular kidney nevertheless, excretes urea, uric acid and injected dyes.

Tubular excretion (of uric acid) is also a prominent feature of renal function in birds and reptiles.

The question of tubular excretion may be summed up by saying that, though dyes, creatinine,⁸ diodrast etc., are excreted by the proximal tubules of the mammalian kidney, such a process is probably of relatively little importance under ordinary circumstances and may be no more than a functional relic inherited from primitive forms. It seems unnecessary to invoke tubular excretion⁹ to explain the several phases of renal activity. Nor does such a conception aid greatly in the interpretation of renal disease. Glomerular damage and reduction in filtration go hand in hand with the ability of the kidney to clear the blood of urea (p. 403). Also, in acute nephritis the glomeruli are chiefly involved in the inflammatory process, filtration is reduced and retention of urea in the blood may be a pronounced feature; in lipid nephrosis (p. 400), on the other hand, there is little or no detectable injury to the glomeruli whereas the tubule cells show striking degenerative changes, filtration is apparently unimpaired and urea retention (which one should expect were the excretion of this substance an important duty of the tubules) does not occur. On the other hand

⁸ Creatinine is excreted by the human kidney but not by the dog's kidney.

⁹ Statements regarding tubular excretion are not intended to refer to such substances as ammonia and hippuric acid which are formed by the kidney and passed into the urine. Excretion of these substances is an important renal function (p. 391).

it is quite possible if not probable that in chronic kidney disease involving the glomeruli (glomerulonephritis) the primitive excretory functions of the tubules may be called upon to play a much more important rôle than they do in health.

THE REGULATION OF THE URINARY FLOW

(The volume of the urine may be increased by (1) increased rate of filtration, (2) reduced rate of reabsorption, or (3) by a combination of both. Reduction in urinary volume results from corresponding changes in a reverse direction. It should be remembered that a relatively slight percentile alteration in (1) or (2) will cause a relatively great change in the urine volume. If, for instance, the quantity of the reabsorbed fluid remains constant but filtration is increased by only 1 per cent, say, from 100 to 101 liters in twenty-four hours, the urine flow (taking 1500 cc. as the average daily excretion) will be increased by over 60 per cent. A reduction of 1 per cent in the quantity of reabsorbed fluid (filtration remaining constant) will increase the urine volume to a comparable extent.

(1) **FACTORS WHICH INFLUENCE THE FILTRATION RATE.** (a) Variations in the size of the filtering surface. Richards and Schmidt showed that the number of patent glomeruli in the kidneys of frogs varied from time to time under various nervous and chemical influences (fig. 177). Nor is the number of open capillaries in an active glomerulus fixed. At one moment, under a certain condition, only a few loops may be patent, at another moment, under changed conditions, the glomerulus appears as a red ball with all its vessels dilated (Ekehorn). The intermittence of function demonstrated for the amphibian glomerulus probably does not apply to the mammalian kidney. The evidence indicates that in the rabbit, the dog and the human subject the glomeruli are continuously active (White; Shannon; Smith and associates).

(b) Changes in pressure within the capillary loops. Such may result from alterations in caliber of the afferent or efferent vessels (dilatation of the former or constriction of the latter will increase the glomerular pressure), or from changes in the systemic blood pressure. A rise in general arterial pressure, apart from any vascular changes within the kidney itself, will increase both renal blood flow and glomerular pressure. According to Erlanger and Hooker the magnitude of the pulse pressure is also an important factor in renal activity (see also p. 132).

(c) Changes in the renal blood flow. The extent to which a rise in glomerular pressure alone can augment filtration is limited by the fact that as fluid is expressed from the capillary loops the contents of the latter undergo a considerable reduction in bulk. As a consequence, the intra-capillary pressure tends to fall and the osmotic pressure to rise. These effects will, of course, slow the filtration rate. It has been estimated that under ordinary circumstances from about 20 to 25 per cent of the plasma is filtered from the blood in its passage through the glomerulus. The blood within the capillary must therefore undergo renewal at a certain rate in order to maintain filtration at a high level.

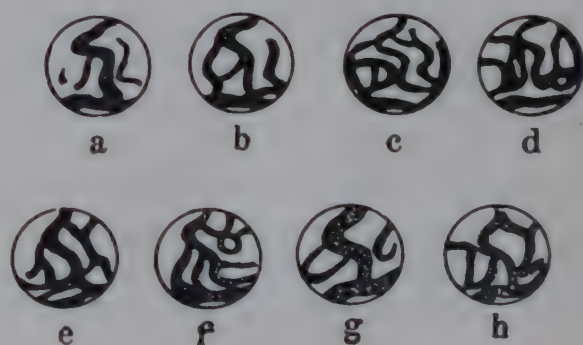


FIG. 177. Variations in capillary pathway within a single glomerulus. *a*, 5 minutes before an intravenous injection of 0.1 cc. of 10 per cent glucose: blood flow very slow. *b*, 10 minutes after glucose: blood flow still slow. *c* and *d*, 25 and 30 minutes after glucose: blood flow more rapid and cells less closely packed. *e*, 45 minutes after glucose: blood flow slow, cells densely packed: *f*, 9 minutes after intravenous injection of 0.5 cc. 0.7 per cent NaCl: flow more rapid and cells less dense. *g*, immediately after injection of 0.1 cc. adrenaline 1/100,000 blood flow very slow. *h*, 5 minutes after *g*: blood flow rapid. (After Richards and Schmidt.)

The blood flow through the human kidneys under various conditions has been measured by Smith and his associates by means of the diodrast plasma clearance method and obtained a value of around 1300 cc. per minute (both kidneys) or more than a quarter of the cardiac output. Diodrast, an iodine compound, when in low concentration in the plasma undergoes complete clearance, i.e., it is completely removed from the plasma in a single passage of the blood through the kidney. This substance is excreted largely by the tubules, only a small fraction (approximately 16 per cent) being filtered through the glomerulus. Knowing the amount excreted in the urine within a unit of time and the concentration in the plasma, it is a simple matter to calculate the quantity of blood which has passed through active renal tissue. By way of illustration let us take some representative figures. Say that 700 milligrams of dio-

drast are excreted in the urine each minute and each cubic centimeter of plasma contains 1 mgm.; obviously then in the delivery of the 700 mgm. of diodrast 700 cc. of plasma, or about 1300 cc. of blood, must have passed per minute through the kidneys.¹⁰ The human kidneys together weigh about 300 grams, a blood flow of 1300 cc. per minute therefore amounts to over 4 cc. per gram of renal tissue per minute. This figure is in close agreement with that obtained by direct determinations of renal blood flow made upon laboratory animals, the minute flow for the rabbit being given as between 4 and 7 cc. per gram of tissue.¹¹ If the filtration rate as well as the plasma flow is known, the percentage of the plasma filtered from the blood can be readily calculated. Thus the filtration rate, as determined by the inulin method, is around 125 cc. per minute, therefore the plasma in passing through the glomerular capillaries loses about $(\frac{125}{700} \times 100 =)$ 18 per cent of its bulk. This figure is not constant but, as indicated above, is altered by several conditions, e.g., the pressure within the glomerular capillaries, the rate of blood flow through them, etc.

Some of the more interesting physiological features of the blood supply to the kidney may be mentioned here. The renal circulation possesses a greater degree of independence in respect to the general circulation than most other vascular areas. There is little definite information concerning the basis of this autonomy, though the juxta-glomerular apparatus (p. 379) is suspected of playing a dominant rôle; the controlling mechanism is not impaired by denervation of the kidney. The renal vessels do not share in the reflex vasoconstriction which follows hemorrhage nor in other reflexes initiated from the carotid sinus or aortic arch. Reactive hyperemia (p. 271) which is readily induced in other vascular areas, e.g., skin

and cardiac muscle, is not shown by the renal circulation, nor is denervation of the kidney followed by augmentation of the blood flow. Certain fever-producing agents (pyrogens), such as typhoid vaccine, however, cause a pronounced increase in renal blood flow.

(d) *Changes in protein content* and so in the osmotic pressure of the plasma (p. 381).

(e) *Changes in the rate of reabsorption.* In the absence of any other means of facilitating the progress of the filtered fluid through the long and narrow tubules to the renal pelvis, a high pressure within Bowman's capsule would be required (80 mm. Hg, according to Brodie). There would then be the need for a glomerular blood pressure sufficient not only for filtration but for the creation of this high intracapsular pressure in order to overcome the resistance in the urinary channels. Reabsorption renders such a pressure unnecessary. In the first place a certain proportion of the fluid need be driven only as far as the proximal convoluted tubule where the reabsorption process commences (p. 384). The passage of the remainder of the filtrate beyond this to the distal convoluted tubule is facilitated by the withdrawal by reabsorption of the layer of fluid in immediate contact with the wall of the tubule. In the passage of fluid along an ordinary capillary tube the layer of fluid in contact with the wall of the tube is stationary; friction develops between this and the next layer and between successive layers toward the axis of the stream. As a result of the reabsorption process frictional resistance is reduced to a minimum. When, on the other hand, tubular function is impaired the development of a high intracapsular pressure is required in order to overcome the increased resistance and drive fluid along the tubule. Filtration is materially reduced in consequence.

(2) THE REGULATION OF REABSORPTION. The chief factors are: (a) the rate of flow along the tubules; the faster the flow, the shorter is the time permitted for reabsorption to occur. (b) When sufficient time is allowed, the osmotic pressure of the fluid in the tubules is the factor which brings reabsorption to an end. As a result of the reabsorption from the filtrate of a more dilute fluid than the filtrate itself, concentration of non-threshold substances in the tubular fluid and a rise in its osmotic pressure must occur. Reabsorption ceases when the epithelial cells are incapable of performing the work necessary to overcome the osmotic resistance. Back diffusion of low threshold substances tends to increase, how-

¹⁰ In order for a substance to serve as a means of measuring the plasma flow it must not be stored by the kidney nor taken up by the blood cells. All the evidence indicates that in the human subject, at least, these requirements are for all practical purposes fulfilled by diodrast.

¹¹ Van Slyke and associates obtained values in unanesthetized dogs of from 2 to 10 cc. per gram per minute. The bloodflow was calculated from the urea N excretion per minute in milligrams (E) and the difference between the urea contents of renal arterial (A) and renal venous (R) bloods in milligrams per cubic centimeter. Thus,—

$$F = \frac{E}{A - R}$$

where F = blood flow in cubic centimeter per minute.

ever, as the concentration rises. The concentration of the solute in the interstitial fluids, i.e., the fluids on the other side of the tubular membrane, is a factor of equal importance. As this concentration approaches that of the tubular fluid, reabsorption becomes progressively lower and ultimately ceases.

In the reabsorption of a substance from the filtrate there is a maximum rate which may be expressed in milligrams per minute and is conveniently designated by the symbol *T_m*. (maximum transfer). Thus the maximal rate of reabsorption of glucose, or *glucose T_m*, amounts to about 320 mgm. per minute in man. It is determined by raising the plasma glucose concentration and measuring simultaneously the rate of filtration (inulin clearance method, p. 404) and the excretion of sugar in the urine. When the filtration rate of glucose rises above the maximum rate or reabsorption, glycosuria occurs.

The reabsorption process is not subject to direct nervous influences, nor, of course, is the purely passive process of filtration. The effects upon renal function exerted by the nervous system are the result of its action upon the circulation and, possibly, upon the activity of certain ductless glands. In the latter connection the results of Theobald and Verney may be cited. These observers found that afferent nerve stimulation caused inhibition of water diuresis of the completely denervated kidney. They suggest that the antidiuretic effect is brought about through pituitary secretion (p. 390). The pituitary hormone exerts its antidiuretic effect most probably by increasing reabsorption.

DIURESIS

Substances such as *caffeine*, *sodium sulphate*, *urea*, *mercurial salts*, *acidifying salts*, e.g., CaCl_2 , NH_4Cl , and under certain circumstances *digitalis*, act as powerful *diuretics*. *Caffeine* appears to exert its action in part at least by causing renal vasodilatation. *Caffeine* increases the chloride concentration of the urine, and lowers the concentration of urea; but the absolute amount of the latter substance excreted is increased (Verney and Winton). The action of *sodium sulphate* is ascribed by Cushny chiefly to reduced re-absorption. Since the epithelial cells are relatively impermeable to sulphate, it increases the osmotic pressure of the fluid within the lumen of the tubules; the work demanded for the reabsorption of the usual quantity of fluid exceeds the capacity of the tubular epithelium. According to Eadie and his associates sulphate also increases the renal blood flow and the filtration rate. *Urea*, and the *ammonium salts* which

are reconstituted in the body into urea, act as diuretics in a similar manner. Urea may also increase the filtering surface, more glomeruli becoming active. The *polyuria* of diabetes is due to the high concentration of sugar in the glomerular filtrate; as in the case of sulphate diuresis the osmotic pressure level at which re-absorption ceases is reached sooner than under normal circumstances. The polyuria and glycosuria following the administration of *phloridzin* is due to the paralysis of tubular function. The action of this drug is mainly upon the proximal tubules. *Salysrgan*, a mercurial diuretic, probably acts also by depressing re-absorption. *Digitalis* has practically no diuretic action in a healthy person nor in a patient suffering from cardiac failure but with no edema. On cardiac edema, but not on other types, the effect is striking, marked diuresis occurs and the edema is reduced. The result is undoubtedly due to the specific action of the drug upon the failing circulation. *Alcohol* is a powerful diuretic; the diuresis resembles water diuresis; it is antagonized by pituitrin.

Water and saline diuresis

The ingestion of large quantities of water by a normal person causes the urine output to increase many-fold. The extra water is eliminated within 4 hours or so, and the greater part of it within 2 hours. The diuresis does not commence until from 30 to 60 minutes after the water has been drunk. Normal or hypertonic saline given by mouth, on the contrary, causes relatively little effect upon the urinary flow. Normal or hypertonic saline or water given intravenously causes profuse diuresis (p. 382). The diuretic effect of the oral or intravenous administration of water is much less in anesthetized than in conscious animals. Water diuresis is also inhibited (as a result apparently of the release of the pituitary antidiuretic substance) by muscular exercise, by afferent nerve stimulation (Theobald and Verney) and in certain emotional states.

The urine after water drinking is very dilute, the specific gravity ranging between 1.000 and 1.002, i.e., considerably lower than that of the plasma; the percentage of chloride as well as the total quantity excreted is greatly reduced. The urea percentage is also reduced, though the absolute quantity excreted may be doubled.

The processes involved in the diuresis following the ingestion of water are complex and not fully understood; the phenomenon has been the subject of numerous investigations. In the experiments of Priestley, from 2 to 3 liters of water were drunk within a few minutes. The diuresis was accompanied by an increase of only about 2

per cent in the water of the blood, and this is quite inadequate to explain the large quantity of urine excreted on the basis of dilution of the plasma proteins. Nor could a rise of 2 per cent in the total blood water account for more than a small fraction of the water ingested. Furthermore, the blood dilution actually passes its maximum and is declining again before the diuresis commences. In these experiments, the results of which have been confirmed in general by others, the blood chloride fell by 5 per cent and the electrical conductivity of the plasma to a corresponding extent; obviously such a reduction in chloride could be only partly accounted for by the blood dilution, and the fall in urinary chloride is evidence that the salt does not escape through the kidney. It appears that the great bulk of the ingested fluid leaves the vessels and is followed, or accompanied by salt which serves to preserve the isotonicity of the tissue fluids. Such a migration of salt would account to a large extent for the fall in blood chloride. The load of fluid is subsequently discharged from the tissues in a slow but steady stream and transported to the kidneys.

The delayed onset of the diuresis following the ingestion of water is not due simply to the time required for absorption from the intestine, for a similar delay occurs when the diuresis is caused by the intravenous administration of water.

Inhibition of tubular reabsorption is an important factor in water diuresis; chloride, on the contrary, appears to be reabsorbed more completely. Such urine with its low chloride content resembles that formed by the isolated kidney (i.e., one freed from pituitary control (p. 397)). The diuresis following lesions in the region of the pituitary (p. 739) also resembles the diuresis of water drinking, and the latter, like the former, can be inhibited for several hours by the administration of pituitrin or of acetylcholine which is believed to cause the liberation of the pituitary antidiuretic principle. The chloride content of the urine during the period of inhibition is around the normal level. Pituitary removal in animals increases the output of urine (less water reabsorbed) and increases the absorption of chloride. It has been mentioned, page 389, that afferent nerve stimulation inhibits water diuresis of a denervated kidney. The inhibitory effect must therefore be brought about through the blood stream; Theobald and Verney secured evidence which suggests that the liberation of the antidiuretic principle from the pituitary is the responsible factor.

The foregoing observations suggest that the pituitary hormone is concerned in water diuresis and that it influences the re-absorption of water and salt by the tubule cells. But it is not at present possible to arrive

at any definite conclusion as to the precise manner in which it acts. Suppression of the antidiuretic principle of the pituitary brought about in some way by the passage of the ingested fluid into the tissues, either through the liberation of a tissue hormone or by afferent nerve impulses, is a distinct possibility. Several observations suggest that the pituitary effect is brought about through the nervous system rather than through some change in blood composition acting directly upon the gland. A conditioned diuretic response, for example, can be established in animals, and diuresis can be induced by suggestion in patients during hypnosis; the inhibitory effect exerted by anesthetics, narcotics or emotional states upon water diuresis has been mentioned. Verney and his associates favor this conception, namely, that the diuretic response is the result of the suppression of the secretion of the antidiuretic principle of the pituitary through nerve impulses. The antidiuretic effect will not, of course, be abolished immediately upon the suppression of the pituitary secretion; a certain time will elapse before the quantity of the pituitary principle already present in the circulation is removed. This would account for the delay in onset of the diuresis after the water has been absorbed. As the concentration of circulating hormone becomes reduced the kidney, released from the restraining influence, increases its output. The pituitary reasserts its antidiuretic influence again after the load of tissue fluid has been removed. On the other hand, the experiments of Smirk and Newton indicate that the pituitary is not absolutely indispensable for the production of water diuresis. They claim to have obtained the typical response in animals after removal of the pituitary, hypothalamus and all brain tissue above the tentorium cerebelli.

Smirk and associates have also carried out a number of instructive experiments upon water diuresis in man and animals. By means of an ingenious procedure they were able to weigh separately the abdomen and limbs of a human subject or of an intact animal after water drinking. They took the progressive reduction in weight of the abdomen and the increase in weight of the limbs as indices of water absorption from the intestinal tract and water deposition in the tissues, respectively. The weight of the abdomen was found to increase immediately after the water was drunk; it then gradually declined for a period of from 22 to 55 minutes while the leg weight increased. After drinking 1 liter of water the leg weight increased by 1.5 per cent (1 liter was 1.3 per cent of the subject's body weight). This figure agrees closely with one calculated upon the basis that the absorbed water was distributed generally throughout the tissues of the body. The leg weight gradually declined during the diuresis. The decline was delayed by pituitrin. Absorption was found to be complete and the dilution of the blood was falling from its maximum before the diuresis commenced. These observers conclude therefore that the diuresis is not simply the result of the blood dilution but that renal activity was

initiated in some other way after practically all the absorbed water had entered the tissues.

REDUCTION IN THE URINARY FLOW

The urinary flow is reduced in muscular exercise, presumably a result of the diversion of blood to the active muscles; in cardiac failure, as a result of the engorgement of the renal vessels and slowing of the blood flow (p. 148); in acute inflammatory conditions of the kidney; in the later stages of chronic nephritis; in fevers and in dehydrated states, or when the fluid intake is reduced. The effect of pituitrin upon the urine volume has been mentioned (see also p. 731).

THE PRODUCTION OF AMMONIA BY THE KIDNEY—HIPPURIC ACID FORMATION

The experiments of Nash and Benedict in 1921 furnished evidence for the renal origin of urinary ammonia. (1) The blood of the renal vein contains 2 or 3 times more ammonia than does the blood of the renal artery. (2) The ammonia of the systemic blood is not altered by conditions which increase the ammonia of the urine (p. 392). (3) In animals the blood ammonia does not rise after bilateral nephrectomy nor in nephritis though the urinary ammonia is often reduced. (4) In diabetic acidosis the blood ammonia is not greater than normal, yet the urinary ammonia is greatly increased.

Urinary ammonia has been thought to be derived mainly from urea and to a less extent from the deaminations of amino acids. However, Van Slyke and his colleagues have shown that glutamine is the chief source. Amino acids furnish a smaller proportion, but none is derived from urea. They found that all the urea removed from the blood by the kidney was excreted unchanged, whereas the glutamine so removed accounted for at least 60 per cent of the urinary ammonia.

The kidney (as well as the liver) conjugates glycocholic and benzoic acid with the production of hippuric acid (benzoyl-glycine). This is a detoxicating process.

THE REACTION OF THE URINE AND THE RÔLE PLAYED BY THE KIDNEY IN THE REGULATION OF THE ACID-BASE BALANCE

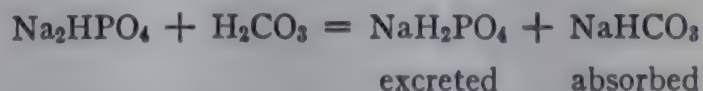
The acidity of the urine may be expressed in two ways, either with regard to (a) *its concentration in hydrogen ions*, i.e., its true acidity, or (b) the total quantity of free acid present as determined by titration with N/10 sodium hydroxide

using neutral red or phenolphthalein as indicator. This measurement, which is expressed as the number of cubic centimeters of N/10 alkali used for the titration, is called the *titratable acidity*.

(a) THE pH OF NORMAL URINE usually lies between 5.0 and 7.0 with a mean of 6.0. The extremes in health are 4.7 and 8.0. The pH of urine is determined mainly by the proportions of the di-basic (alkaline) and mono-basic (acid) phosphates which it contains. The kidney receives blood at a pH of about 7.40 and forms urine with a pH of around 6.0. It accomplishes this by altering the proportions of the acid and alkaline phosphates. The ratio of these in the plasma is $\frac{\text{NaH}_2\text{PO}_4}{\text{Na}_2\text{HPO}_4} = \frac{1}{4}$ whereas in urine with a pH of 6

the ratio is more than reversed, being $\frac{\text{NaH}_2\text{PO}_4}{\text{Na}_2\text{HPO}_4} = \frac{9}{1}$.

When the urine is at its greatest acidity the ratio is 50:1. By this device a large amount of the body's fixed base (Na chiefly, but also K, Mg and Ca) is conserved. The change from di-basic to the mono-basic salt probably takes place during the passage of the urine through the distal tubule. Wearn and Richards found that the glomerular filtrate of frogs was alkaline in reaction whereas the urine was acid. Cushny found that in dogs the injection of di-sodium (alkaline) phosphate increased the acidity of the urine. A portion of the sodium of the injected salt was retained and the resulting acid phosphate was excreted. It was also found that when the di-basic salt was injected into an animal with one ureter partially obstructed (to increase absorption from the tubules) the urine from that side was more acid than was the urine coming from the free ureter. The injection of such substances as sodium chloride or sodium sulphate was found to reduce the acidity of the urine since they caused diuresis, the rapid flow of urine through the tubules curtailing the conversion of di-basic phosphate to the mono-basic salt. The chemical change which probably occurs in the tubules is shown below:



The bicarbonate is reabsorbed by the epithelium of the tubules.

In alkaline urines the pH is determined chiefly by the carbonic acid—bicarbonate ratio $\frac{\text{H}_2\text{CO}_3}{\text{NaHCO}_3}$ (see below). The pH and volume of the urine in health and under usual conditions vary together

and in the same direction; a urine of a small volume being usually of a lower pH than one of larger volume. A urine of average acidity (pH 6.0) may have its pH raised to 7.0 by maximum diuresis but rarely higher than this.

(b) **TITRABLE OR TOTAL ACIDITY.** By this is meant the quantity of acid in excess of basic substances (i.e., the free acid) present in the urine. The greater part of the titratable acid is phosphoric in the form of the mono-basic (chiefly sodium) salt. A small part of the titratable acid is due, however, to free organic acids, uric, lactic, hippuric, etc. The usual amount of titratable acid in a 24-hour specimen of urine lies between 200 and 400 cc. of N/10 standard acid. Its amount, however, depends in health upon several conditions and may be as low as 100 cc. or as great as 600 cc. In severe diabetes it may be 2 or 3 times the latter figure, as a result of the excretion of large quantities of acetoacetic and β -hydroxybutyric acids (acetone bodies).

The total acidity is determined by titrating the urine with N/10 sodium or potassium hydroxide, the result being expressed as the number of cc. of N/10 alkali required to bring 100 cc. of urine to near the neutral point, the precise reaction attained depending upon the indicator used. When the titration is carried out to the pH of blood (7.4) the result obtained has a greater physiological significance than if the urine were exactly neutralized (pH 7.0). In Henderson and Palmer's method neutral red, which turns a brownish red at the normal blood reaction, is used as indicator. When the urine is titrated to the reaction of the blood, the procedure obviously reverses the change in reaction which the kidney had effected during the formation of the urine from plasma. The quantity of alkali added is therefore a measure of the quantity of fixed base which the kidney has saved to the body by the conversion (chiefly) of the di-sodium phosphate to the corresponding acid salt. Frequently, phenolphthalein is used as the indicator in titrations of urinary acidity (Folin's method) but since this indicator turns color (colorless to pink) at a pH of 8.2, it is clear that the result will be considerably higher than when neutral red is employed, and urine which is actually neutral or alkaline, or even blood plasma itself will then have a titratable "acidity."

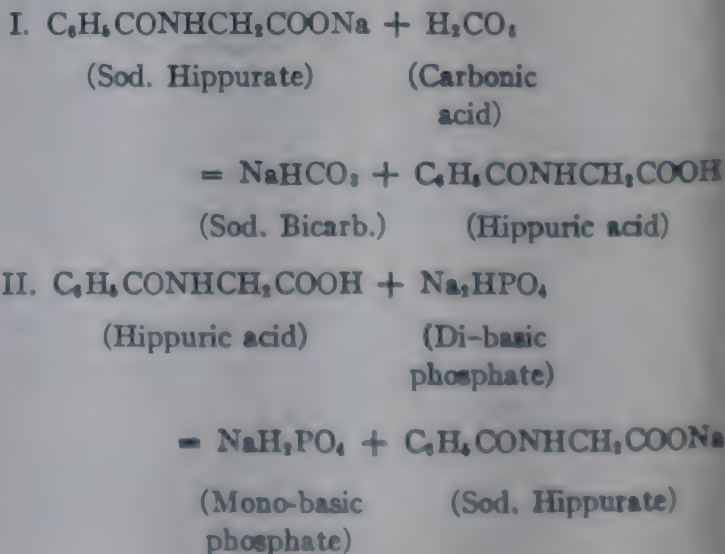
BASE-CONSERVATION BY THE KIDNEY

The stores of base in the body fluids can be replenished only from without. The kidney plays an important rôle in preventing the depletion of these stores. One important method of conservation, namely, the conversion of the di-basic to the mono-basic phosphate, has just been mentioned. For every molecule of alkaline phosphate converted in the tubules of the kidney to the acid salt one molecule of NaHCO_3 is returned to

the body's store of alkali. Or, put in another way, about 40 per cent of the base bound to phosphoric acid in the plasma is saved by the conversion of the di-basic phosphate to the mono-basic form.¹²

Another means of conserving base is the retention of part of the base combined in the blood with organic acids and the excretion of the latter in the free state; this though of little importance in health is of great importance in disease. Organic acids may pass into the urine in three ways: (a) in combination with fixed base (urates, hippurates, lactates, etc.), (b) in combination with ammonia, or (c) free. In highly acid urines according to Henderson and Palmer uric acid is 91 per cent free, lactic 12 per cent and hippuric 8 per cent. The abnormal organic acids acetoacetic and β -hydroxybutyric formed in diabetes though combined with fixed base to the extent of 100 per cent in the plasma with consequent reduction in the alkali reserve are excreted free in considerable quantities (acetoacetic 5 to 11 per cent, β -hydroxybutyric 20 to 55 per cent). Any acid excreted in the free state obviously represents a clear saving of the body's alkali. Palmer and Van Slyke state that the measurement of the increase in the excretion of total organic acids in diabetes is a reliable approximate guide to the quantity of acetone bodies (acetoacetic and β -hydroxybutyric acids) produced. The

¹² Hendrix and Sanders have shown that not only is base from the alkaline phosphate saved to the body, but that base from injected salts bound to acids as strong as hippuric is retained. The retention, it is believed, is effected not by the excretion to any extent of free hippuric acid, but by the substitution in the kidney of fixed base by ammonia as well as by the conversion of the di-basic phosphate to the mono-basic form. Such conversion is represented by the following reactions—



The base of salts of stronger acids such as sulphuric is not retained.

total quantity of organic acid (bound and free) excreted daily by a healthy man is between 240 and 600 cc. of N/10 organic acid (average of 6.0 cc. per kg. of body weight).

The third method by which fixed base is saved by the kidney is in the manufacture of ammonia (p. 391) for the neutralization of acids. The kidney separates certain acid radicals from the fixed bases with which they were combined in the plasma, joins them to ammonia, and excretes them as ammonium salts. In order therefore to arrive at a true estimate of acid excretion and the base saved to the body, the quantity of the ammonia excreted should be added to that of the titratable acid (titration to 7.4). The acid + ammonia value represents what may be termed the *base economy* exercised by the kidney. In health the daily excretion of ammonia amounts to from 300 to 500 cc. of N/10 ammonia. In severe diabetes it may be ten times this value. The hydrogen ion concentration, titratable acidity and ammonia of the urine usually vary together and in the same direction, though there is no exact proportional relationship. All three are determined by the relative concentrations of basic and acid radicals in the plasma. The value of the acid + ammonia excretion may therefore be employed as an approximate index of the lowering of the alkali reserve in such conditions as diabetes. The *ratio* of ammonia excretion to titratable acid in health

is usually 1 or over $\left(\frac{\text{NH}_3}{\text{titratable acid}} = 1 \text{ to } 2.5 \right)$.

In moderate degrees of kidney disease in which the urea concentrating function is impaired the ratio is low (0.1 to 0.7) owing to the fact that the power of the kidney to form ammonia is depressed while the excretion of acid is little altered. When however the renal insufficiency becomes extreme, the ratio may be higher than the impairment of renal function would lead one to expect. The rise in the ratio is due, not to an increase in the output of ammonia, but to a reduction in the excretion of acid. In the nephrotic type of nephritis in which there is no impairment of urea excretion the production of ammonia is not interfered with and the ratio is normal.

Fixed base enters the urine other than in combination with phosphoric acid. Sulphuric and hydrochloric acids formed during protein catabolism differ from phosphoric acid in that they are not excreted in the free state except in infinitesimal amounts but carry with them their full base equivalent, appearing in the urine as the neutral salts of either fixed base (NaCl , Na_2SO_4) or of ammonia (NH_4Cl , $(\text{NH}_4)_2\text{SO}_4$).

The *free carbonic acid* in the urine is small in amount (4.2 vols. per cent Gamble) and remains practically stationary at that of the plasma of the renal blood, passing into the urine by simple diffusion. It does not vary in amount with changes in urinary pH. The bicarbonate content of the urine, on the contrary, varies directly with the pH; in alkaline urines its quantity is large (up to 8 grams per liter), whereas in highly acid urines its quantity is negligible (0.02 gram per liter). When, therefore, the alkali reserve of the blood is normal or low, the urine is acid and practically no base is lost as bicarbonate. When, on the other hand, the bicarbonate of the plasma is above normal the urine is alkaline and large quantities of base pass into the urine as bicarbonate. Since the free carbonic acid remains unchanged at varying urinary pHs while

the bicarbonate content varies, the ratio $\frac{\text{H}_2\text{CO}_3}{\text{NaHCO}_3}$ in

the urine varies with changes in pH.¹³ The ratio in urine on the acid side is from $\frac{1}{3}$ to $\frac{1}{4}$, whereas in neutral or alkaline urines it is from $\frac{1}{7}$ to $\frac{1}{100}$. The small quantities of free carbonic acid and bicarbonate present in acid urines render these "buffers" of negligible importance in determining the urinary pH as compared with the alkaline and acid phosphates. In alkaline urine the reverse is true, the carbonic acid—bicarbonate ratio being of primary importance.

The influence of starvation, diet, and of acid and alkali ingestion, upon urinary acid

Starvation increases the titratable acidity and ammonia, and lowers the pH of the urine. After exhaustion of the glycogen stores increased protein breakdown occurs with the production of phosphoric and sulphuric acids. As a result of the incomplete combustion of fat acetoacetic and β -hydroxybutyric acids are formed and excreted.

Diet. Cereals, meat and fish increase the titratable acid and ammonia of the urine and lower the pH. Most fruits (apples, pears, peaches, lemons, oranges, grapes, figs and raisins) contain the salts of organic acids; the acid radical undergoes oxidation in the body, the alkali being liberated. These fruits therefore tend to raise the alkali reserve of the plasma and to reduce the acidity of the urine. Plums, prunes and cranberries, on the contrary, increase urinary acidity since they contain benzoic and quinic acids which are converted to hippuric acid in the kidney. The herbivora normally pass alkaline urine, though if starved and so forced to use their body protein or if fed upon flesh, the urine becomes acid. The pH of the urine of men upon a purely vegetarian diet is from 5.30 to 7.48 with a mean of 6.64 instead of the usual mean of 6.0.

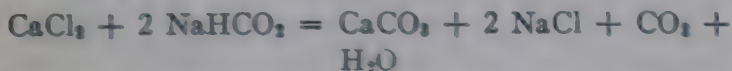
¹³ Since the H ion concentration of a solution containing H_2CO_3 and NaHCO_3 is a function of the ratio of the concentrations of these substances, if H_2CO_3 concentration remains stationary, variations in the concentrations of the other two must be inversely related.

Ingestion of acid and alkaline chemical substances. When acids such as sulphuric or hydrochloric, or acidifying salts (CaCl_2 , NH_4Cl , $(\text{NH}_4)_2\text{SO}_4$) are taken by mouth in large amounts, a reduction in the alkali reserve of the plasma, an increase in the total excretion of phosphate, chiefly of the mono-basic salt, a rise in the titratable acidity and a fall in pH of the urine result. The urinary ammonia increases. The following reaction results from the absorption of hydrochloric acid.



A proportion of the Cl^- radical is excreted in the urine as NaCl and so entails an equivalent loss of fixed base. Some excretion of acid over basic substances is effected by the excretion of a greater proportion of the mono-basic phosphate. This factor, however, is limited since at the usual reaction of the urine 90 per cent of the dibasic phosphate has already been converted to the mono-basic form. Also, the body's available stores of phosphate after a time become exhausted; the excretion of acid by this means must then come to an end. It has been pointed out that normally a most important factor in the elimination of acid radicals and the conservation of fixed base is the production of ammonia by the kidney; after the ingestion of HCl a part of the Cl^- is excreted as the ammonium salt.

Similar changes to those just described follow the ingestion of CaCl_2 or of NH_4Cl in large doses. In the case of calcium chloride ingestion Cl^- displaces HCO_3^- from the bicarbonate of the body fluids according to the following equation.



The NaCl and CaCO_3 are excreted. There is thus a net loss of base from the body; a severe acidosis results. The calcium is excreted mainly in the feces, though it is possible that a proportion is also deposited in the bones, since calcium in the form of the chloride when fed to dogs cannot all be recovered from the excreta. As in the case of HCl ingestion, Cl^- is also excreted in the urine combined with ammonia.

The acidifying effect of NH_4Cl is probably due to the conversion of NH_4 to urea, the Cl^- radical being freed. When 20 grams or so of NH_4Cl are administered the urinary excretion of urea and of sodium chloride rises abruptly. The reaction is shown as follows:



The HCl then reacts with bicarbonate of the plasma with the production of sodium chloride and carbonic acid. The passage of the large quantities of base into the urine when calcium chloride or ammonium chloride are administered requires the excretion of large quantities of water. These two salts therefore act as powerful diuretics and agents for the removal of edema fluid. When large quantities of acid-sodium phosphate are ingested, though there is a great increase in the titratable acidity of the urine, no change in ammonia excretion

occurs. Since this salt can be excreted as such there is no call apparently for the production of ammonia for the conservation of base such as occurs after the ingestion of hydrochloric and other acids.

The effects of the *administration of alkalis* are, as might be expected, the reverse of those following the ingestion of acid substances. Large doses of bicarbonate augment the alkali reserve, reduce the excretion of total phosphates, and increase the proportion of those in the di-basic form. The excretion of the titratable acid plus ammonia falls while the bicarbonate content and pH of the urine rise. Though large doses (45 grams daily) of bicarbonate are required to render the urine alkaline and keep it so, a wave of urinary alkalinity will result from the administration of much smaller doses. Palmer and Henderson make use of this fact in their *bicarbonate tolerance test* for reduction in alkali reserve. Four grams of sodium bicarbonate when administered to a normal person cause a perceptible rise in urinary pH, whereas larger doses are required to produce a similar effect in one with a lowered alkaline reserve. A similar clinical test has been devised by Sellards. These tests are of value in some conditions, but in nephritis the power of the kidney to excrete bicarbonate may be impaired, under which circumstances the test would indicate a lower alkaline reserve than actually existed. In diabetes also the test may indicate acidosis in its absence. For these reasons more reliance may be placed upon the test when it is negative (i.e., when it indicates a normal alkaline reserve) than when it is positive. Salts of organic acids—acetates, citrates, lactates—are also alkalinizing in their action; the organic acid radical is oxidized, the base joining with H_2CO_3 to form bicarbonate.

The "alkaline tide" of the urine

Leathes found that the urine passed a short time after rising in the morning was less acid than that formed during sleep. This change in urinary reaction is spoken of as the *morning alkaline tide*. (The urine does not necessarily become alkaline but may only become less acid—an elevation in pH or decreased titratable acidity.) The greater acidity of the night urine over the urine of the early waking hours was ascribed by Leathes to depression of the respiratory center during sleep and the retention of carbon dioxide. The increased pulmonary ventilation which occurred after rising supposedly removed carbon dioxide, the effect upon the acid base balance being reflected in the reduced acid excretion by the kidney.¹⁴

¹⁴ Brunton points out that the acid output per minute, that is, the titratable acidity value multiplied by the urine volume (cubic centimeter) per minute is a more reliable index of acid excretion than simply the titratable acidity per unit volume of urine. The latter may be reduced as a result of diuresis without the actual quantity of acid secreted in a given time being altered.

Leathes found that samples of alveolar air taken immediately upon awakening had a higher percentage of carbon dioxide (6.8 per cent) than those taken an hour or so after rising (CO_2 , 5.7 per cent.) It has been shown by Hubbard, however, that merely awakening causes a rise in urinary pH which may be actually higher than after getting out of bed. Now, it is well known that a change in the reaction of the urine towards alkalinity may be demonstrated by voluntary forced breathing. (If the forced breathing is continued for some time the urine may become alkaline to litmus, the bicarbonate content is increased, the acid + ammonia is reduced and acetone bodies may appear.) Nevertheless, since the morning alkaline tide is more pronounced immediately after waking than later when the exercise of dressing, etc., should increase the pulmonary ventilation, the mechanism underlying the fall in urine acidity is not so simply explained. It is associated in some unexplained way with respiratory changes incident to the return of consciousness.

An alkaline tide also occurs within an hour after a meal—*postprandial alkaline tide*. The titratable acidity and ammonia excretion are reduced and the urinary pH rises.

A rise in the CO_2 tension of the alveolar air was first shown by Higgins to occur almost immediately after taking food. Dodds found the rise to amount to from 2 to 6 mm. Hg, and Van Slyke, Stillman and Cullen observed a corresponding rise in the plasma bicarbonate. These changes—reduced excretion of acid by the kidney and retention of carbon dioxide—have been generally attributed to compensatory adjustments in the acid base balance resulting from the loss of hydrochloric acid in the gastric juice. Dodds also reported a fall in alveolar CO_2 tension in from one to two hours after a meal, which was put down to the secretion of alkali in the pancreatic juice. The view that gastric secretion is the cause of the alkaline tide of the urine was supported apparently by the fact that it was most pronounced after the ingestion of meat—a powerful gastric stimulant—whereas it was much less likely to appear after a meal of carbohydrate or fat. Nevertheless, there are many difficulties in the way of accepting this view. A well-marked alkaline tide following meals has been observed in subjects of achlorhydria. Brunton and Wilson, on the other hand, have produced good gastric secretion in subjects by means of a meal of Bovril without any decrease in the total excretion of acid by the kidney. Brunton and Israels also report that a rise in

alveolar CO_2 tension or an increase in the quantity of CO_2 expired per minute does not, as a rule, occur when a profuse secretion of gastric juice is induced by the injection of histamine. A fall in CO_2 tension after a meal coincident with the calculated time of pancreatic secretion was not observed. Such observations strongly oppose the idea that the rise in alveolar CO_2 tension following meals is a consequence of gastric secretion. It is more likely connected in some way with the drowsiness and the reduction in pulmonary ventilation which occurs at this time. Main attributes it to the removal of the stimulating effect of the hunger contractions on the respiratory center. It is also improbable, on theoretical grounds, that the loss of HCl is a factor, since pancreatic secretion follows so closely upon gastric secretion that one effect would be expected to balance the other. These remarks also apply to the postprandial alkaline tide of the urine. Possible additional factors in the production of the latter are excess of basic over acid radicals absorbed from the food itself or the sparing effect of the meal upon protein catabolism. In some instances the decreased urinary acidity is simply due to diuresis, the acid content per unit volume of urine being reduced without any change occurring in the total acid excretion.

THE VOLUME OF THE URINE

The quantity of urine excreted in 24 hours by a healthy adult under ordinary circumstances is between 1000 and 1800 cc. The normal kidney may, depending upon the requirements at the time, eliminate per hour as little as 25 cc. of fluid or as much as 1200 cc. Usually from 40 to 60 per cent of the total fluid intake of the 24 hours is excreted by the kidneys, but the quantity of urine formed must necessarily vary inversely with the quantity of fluid eliminated by other channels,—lungs, skin and bowels. Diet, the quantity of fluid drunk, environmental temperature and humidity, posture, exercise, mental excitement, weight, age and sex, are among some of the physiological factors which influence the urine volume. The output is greater upon a high than upon a low protein diet, the end products of protein metabolism exerting a diuretic effect. High temperature, especially if accompanied by visible sweating, reduces the urine volume. Muscular exercise has a similar effect. The volume is greater in the recumbent than in the erect posture (p. 382). Young children excrete for their weight from 3 to 4 times more urine than adults. The

urine volume is reduced below the normal in cardiac failure, in fevers, in acute nephritis and in the later stages of chronic nephritis. The volume is markedly increased in diabetes insipidus (p. 739) and in diabetes mellitus. (For the action of diuretics, see page 389.)

The urine of the day (8.30 a.m. to 8.30 p.m.) is normally from 2 to 4 times greater in amount than that secreted during the night (8.30 p.m. to 8.30 a.m.). This ratio holds even though the quantity of fluid drunk during both periods is the same. In normal night workers the ratio is reversed. An increase in the night urine of a day worker to an amount approaching that of the day period should suggest renal insufficiency (*nycturia* or *nocturia*).¹⁵ In many cases of renal disease the night urine exceeds the day urine in volume. The terms *polyuria* and *oliguria* are applied respectively to the excretion of supernormal and subnormal quantities of urine. Total cessation (suppression) of urinary excretion is termed *anuria*.

The influence of the pituitary upon the urine volume is dealt with in Chapter LXL (See also p. 390 and p. 397.)

SPECIFIC GRAVITY OF THE URINE

The specific gravity of the urine under the ordinary conditions of health varies between 1.015 and 1.025 and inversely with the urine volume. A urine of large volume usually has a lower percentage of total solids and consequently a lower specific gravity than one of small volume. Upon a very high fluid intake a urine with a specific gravity of 1.001 may be passed. The urine excreted upon a low fluid intake, or when much fluid is lost through other channels, skin and bowels, may have a specific gravity as high as 1.030. In pathological conditions this relationship between specific gravity and volume does not necessarily hold, for large quantities of urine with a very high specific gravity (1.040 or more) are eliminated in diabetes mellitus, whereas in chronic nephritis a urine of small volume and of low specific gravity (1.010) may be excreted. Though the fluid intake be rigidly restricted a kidney whose function is seriously impaired may be unable to concentrate the urine sufficiently to raise the specific gravity above 1.010 or so. Furthermore, when the fluid intake is high the production of urine of very low specific gravity (1.008 or lower), a feat readily accomplished by the normal kid-

ney, is beyond the powers of a seriously diseased kidney. Variability of function according to the needs of the moment is one of the most pronounced characteristics of the normal kidney. The diseased kidney on the contrary is unable to vary the specific gravity of the urine over a wide range; its ability to alter the volume of the urine is also very greatly impaired. The specific gravity of the urine in health is directly proportional to the concentration of its dissolved solids (chiefly chlorides and urea).

A rough method of determining the total urinary solids is to multiply the last two figures of the specific gravity by 2.66 (Long's coefficient). This gives the quantity of total solids in grams per liter. This method is not reliable for some pathological urines, since different substances vary in the extent to which they contribute to the specific gravity of a solution; it is clear that should the urine contain abnormal constituents (albumin, sugar) or should the proportions of its normal constituents be altered greatly, the relationship between total solids and specific gravity just expressed will not hold. Less than 1.5 grams of NaCl, for instance, will produce as great a rise in specific gravity of the urine as nearly 4 grams of albumin. The latter unless present in relatively large quantities will therefore have little effect upon the urinary specific gravity. The following table (after Albarran) gives the amounts of several substances which are required to be added to a liter of urine in order to raise its specific gravity 0.001:

	grams
Urea.....	3.6
Glucose.....	2.7
Acid sodium phosphate.....	3.8
Sodium chloride.....	1.47
Albumin.....	3.9

COMPOSITION OF THE URINE

In the following table are given figures for the average amounts of inorganic and organic solids in 1000 cc. of urine of a healthy adult on an ordinary mixed diet. The total solids amount to from 40 to 50 grams per liter, the urea constituting about one-half of this.

I. Inorganic constituents

	Volume 1000 cc. grams
(a) Chloride expressed as NaCl.....	9.0
(b) Phosphorus expressed as P ₂ O ₅	2.0
(c) Total sulphur expressed as SO ₃	1.5
(d) Sodium expressed as Na ₂ O.....	4.0
(e) Potassium expressed as K ₂ O.....	2.0
(f) Calcium expressed as CaO.....	0.2
(g) Magnesium expressed as MgO.....	0.2
(h) Iron.....	0.003

¹⁵ An increase in the volume of night urine above 500 cc. and with a specific gravity less than 1.018 is usually defined as *nycturia*.

II. Organic constituents

ZNOUS.

..... 25.0 grams containing, approximately, 10.0 gram nitrogen

nia..... 0.6 gram containing, approximately, 0.4 gram nitrogen

cid..... 0.6 gram containing, approximately, 0.2 gram nitrogen

nine..... 1.5 grams containing, approximately, 0.5 gram nitrogen

etermined

ogen¹⁸..... 0.6 gram

total..... 11.7 grams nitrogen

ea, ammonia, and the inorganic and sulphates (pp. 509 and 551) vary with content of the diet whereas the cre- and neutral sulphur, particularly the e little affected by the level of the pro- e (see also table 48, p. 550).

ORGANIC SUBSTANCES PRESENT IN SMALL QUANTITIES OR MERELY IN TRACES:

ments, e.g., urochrome and urobilin, (traces of the latter only).

gar, minute amounts (2 to 3 mg. per cent) of fermentable sugar are found in the urine in 50 per cent of normal persons after the noon meal (Harding and associates).

etty acids; aceto-acetic and β -hydroxybutyric acids.

arbonates, bicarbonates and free carbonic acid.

acin and mucin-like substances.

astase.

rus is found in the urine largely combined with sodium as the *mono-sodium* and *di-phosphates* NaH_2PO_4 and Na_2HPO_4 , and to a lesser extent with potassium to form the *potassium salts* of this mineral. About three-fourths of the total urinary phosphorus exists in these forms. A small quantity is possibly present as $\text{NH}_4\text{H}_2\text{PO}_4$. The remaining quarter of the total phosphate is present as salts of the *alkaline earths*, calcium and magnesium, as $\text{Ca}(\text{H}_2\text{PO}_4)_2$ and $\text{Mg}(\text{H}_2\text{PO}_4)_2$. These earthy phosphates are insoluble in alkaline urine and are precipitated (phosphate deposit) when, as a result of bacterial action the urea of urine which has stood for some time after voiding becomes decomposed with the formation of ammonia. Infection of the genito-urinary tract may for the same reason produce an alkaline urine which is clouded when voided by precipitated phosphates. In perfectly healthy persons urine which, as a result of a diet rich in alkaline carbonates, is alkaline in reaction may be cloudy when passed owing to the production of the insoluble phosphates of calcium and magnesium $\text{Ca}_3(\text{PO}_4)_2$ and $\text{Mg}_3(\text{PO}_4)_2$. The condition is called *struvite*.

posit) when, as a result of bacterial action the urea of urine which has stood for some time after voiding becomes decomposed with the formation of ammonia. Infection of the genito-urinary tract may for the same reason produce an alkaline urine which is clouded when voided by precipitated phosphates. In perfectly healthy persons urine which, as a result of a diet rich in alkaline carbonates, is alkaline in reaction may be cloudy when passed owing to the production of the insoluble phosphates of calcium and magnesium $\text{Ca}_3(\text{PO}_4)_2$ and $\text{Mg}_3(\text{PO}_4)_2$. The condition is

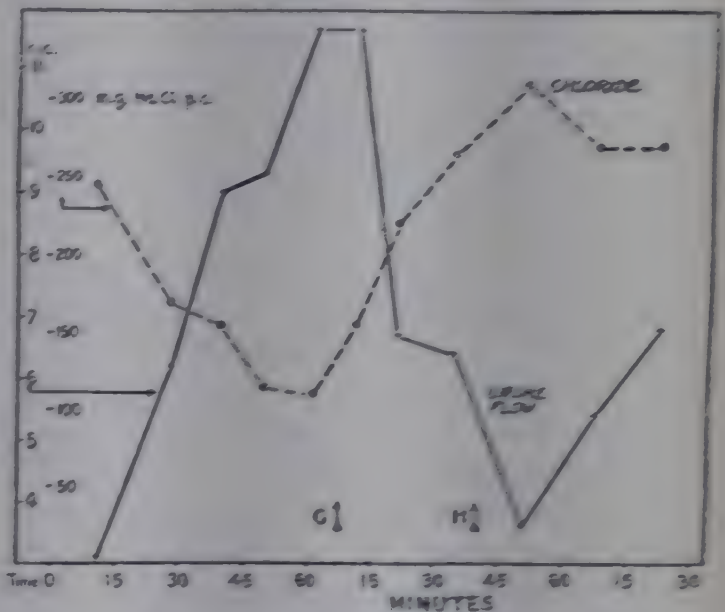


FIG. 178. Heart-lung-kidney preparation. The continuous line represents the rate of urine flow in cubic centimeters per fifteen minutes, the broken line the chloride concentration in the urine. The polyuria and fall in chloride concentration of the urine characteristic of the preparation are clearly shown. At G the head of another dog was included in the perfusion circuit, so that the blood passed through the pituitary as well as through the heart and kidney. A pronounced fall in urine volume and a rise in chloride concentration then occurred. Removal of the head (at H) was followed by a return of the polyuria and a fall in chloride concentration. (After Verney.)

called *phosphaturia* and is quite physiological. The relative proportions of the mono-basic and di-basic phosphates determine the hydrogen ion concentration of normal urine (p. 391). The urinary excretion of inorganic phosphorus is determined by the level of the plasma inorganic phosphorus.

The total phosphate content of the urine is increased under several conditions,—lowered alkali reserve, starvation, high protein diet, severe muscular exercise, in gout and following the administration of large doses of parathyroid extract. It is increased by such diuretics as sodium nitrate and sulphate, and by calcium and ammonium chlorides, but not by water diuresis.

The urinary P is low in the morning but rises in the later hours of the day, reaching a maximum in the night urine. Though the great part of the urinary P is derived from the inorganic P of the plasma, a small part (6 per cent) is organic (glycerophosphates, hexose-phosphates, nucleotides). The kidney is rich in *phosphatase* (p. 716) yet it does not seem that any considerable part of the inorganic P of the urine results from the action of this enzyme upon organic phosphorus compounds of the plasma. The urinary P is *reduced* in pregnancy; when the alkaline reserve is high, in renal insufficiency, tetany and in certain bone diseases. Insulin causes a marked fall in the urinary P for the first six hours following the injection, and a rise for the next six hours. The work of Brull and Eichholtz suggests that the pituitary or hypothalamic region of the brain is concerned in the excretion of inorganic P by the kidney. This was suppressed by removal of the gland or by injury to the tuber cinereum, yet no corresponding change in the level of plasma P (organic or inorganic) occurred¹⁷.

The *chloride* of the urine (chiefly in the form of NaCl) is derived almost solely from the chlorides of the food. The concentration of chlorides in normal urine varies from 0.5 to 2.0 grams (as NaCl) per 100 cc. as compared with about 0.6 per cent in the plasma. Chloride is a high threshold substance and in prolonged starvation or upon a salt-free diet, though the urine may be practically chloride-free, the chloride of the blood remains at or but slightly below the normal level. When chloride is lost through vomiting, the urinary chloride is reduced: the Cl lost in the vomitus being derived from the blood NaCl, results in an excess of base (Na) being left in the plasma; this combines with H_2CO_3 to increase the bicarbonate reserve. In pneumonia, cardiac failure or renal disease with edema, intestinal obstruction, severe diarrhea, and many acute febrile conditions the urinary chlorides are markedly reduced. In lobar pneumonia after the injection of large quantities of sodium chloride only small quantities appear in the urine; the injected salt is retained until after the crisis.

The experiments of Verney and Starling indicate that the posterior lobe of the pituitary gland

exerts a specific effect upon the urinary excretion of chloride by the kidney. These observers found that a kidney, perfused by means of a heart-lung preparation (heart-lung-kidney preparation) excreted large quantities of urine with a very high chloride concentration. The addition of pituitrin to the blood circulating through the organ increased the urine volume; the percentage of chloride in the urine and the total quantity excreted increased. Verney also studied this question upon a heart-lung-kidney preparation in which the blood could be switched at will through the legs or through the head of another animal. In the former instance, the urinary secretion was profuse and of low chloride concentration. When the blood was passed through the head the secretion of water was reduced and the percentage of chloride, and in some instances its absolute amount, rose (fig. 178). Something had evidently been added to the blood during its passage through the head which brought about this effect. If the pituitary had been removed previously the incision of the head and neck in the circulation was without influence upon the chloride excretion (see also Diabetes Insipidus, pp. 731 and 739).

The maximal concentrating power of the kidney for chloride is 0.333 molar. Pituitrin is not capable of raising the chloride concentrating power of the normal kidney above this maximum value.

Sulphur occurs in the urine in three forms: (a) *inorganic sulphates*, (b) *etheral sulphates*, and (c) *neutral sulphur* (see p. 585).

Urochrome (Thudichum) is the normal urinary pigment. Its chemical constitution and the nature of its precursor are unknown. Its output was found by Drabkin to be remarkably constant from day to day under the ordinary conditions of health. The output is independent of diet but bears a relation to the level of the basal metabolism. It is therefore endogenous. In fevers, hyperthyroidism, and as a result of elevating the metabolic rate by the administration of thyroxine or adrenaline its output is increased. The output of urochrome is also increased by tissue breakdown, by starvation or by the administration of acids. Thyroid extirpation reduces its elimination below the normal level in animals, and to the normal level in subjects with exophthalmic goiter.

¹⁷ Except in the alkalosis and hyperphosphatemia of pyloric stenosis when the urinary P is increased.

CHAPTER XXXVII

THE PATHOLOGICAL PHYSIOLOGY OF KIDNEY DISEASE MICTURITION

Classification of kidney diseases

A logical classification of kidney disease would be based upon the nature (inflammatory or degenerative) and the site (glomeruli, tubules or both) of the renal injury, and which would make a correlation to be established, through knowledge of renal physiology, between such injury and the signs and symptoms of the disease. An ideal is impossible of attainment, for though a certain part of the renal structure at one time bears the brunt of the disease, there is a tendency for other parts of the kidney to become secondarily involved, if not in anatomical changes, at least in function. For this reason, as well as from the fact that extrarenal factors (cardio-vascular) may become disturbed to such an extent as to affect renal function, the signs and symptoms of chronic kidney disease are extraordinarily variable; mixed forms of nephritis rather than pure types are common. Nevertheless, a classification based upon the nature of the primary pathological process (inflammatory, degenerative, arteriosclerotic) and the type of renal structure primarily affected will be given. Where possible an attempt will be made to explain signs and symptoms by the application of physiological principles. There are three main types of renal disease:

Glomerulo-nephritis is essentially inflammatory in nature, and the glomeruli are primarily affected.

The *nephroses* are the result of a degenerative process involving the tubules.

Arteriosclerotic kidney disease. The large and small renal vessels are the seat of sclerosis.

GLOMERULO-NEPHRITIS

Glomerulo-nephritis is seen in an acute and a chronic form.¹ Though the chronic type is usually thought to be nearly always initiated by the acute disease, the latter may have been so mild as to have escaped notice. So, chronic glomerulo-nephritis often appears to have arisen *de novo*. The acute disease, and so the chronic form into which it merges, is thought to be usually due to a subacute form—a transition stage between the acute and chronic forms—is recognized.

to the toxin of some streptococcal or pneumococcal infection, e.g., sore throat, scarlet fever, influenza, etc.

ACUTE GLOMERULO-NEPHRITIS

In the acute disease the glomeruli show inflammatory changes which vary in intensity in different cases. When the disease is severe, the following histological picture is seen. Great numbers of the glomerular capillaries are dilated and filled with a coagulated exudate containing a few leucocytes but almost free from red cells. These capillary plugs completely obstruct the flow of blood through a large proportion of the glomeruli. The endothelial cells of the capillaries according to most pathologists show active proliferation, producing masses which project into the vascular lumina. The entire tuft is swollen and may almost fill Bowman's capsule. There is often an exudation of leucocytes into the interstitial tissue around the glomeruli. Bowman's capsule and the tubules contain masses of exudate and red cells, but the tubular epithelium itself, shows little abnormality as a rule, beyond some slight cloudy swelling or fatty change.

Such a severe reaction must of course if wide spread cause a high degree of renal insufficiency. The following are among the chief features of the disease: retention in the blood of non-protein nitrogenous products (p. 402); edema; hypertension (p. 128) with perhaps cardiac dilatation; acidosis; anemia; hematuria; albuminuria and casts (hyaline, blood, granular and epithelial), and the passage of a small quantity of urine with a high specific gravity. The majority of cases are much milder than this but all degrees of severity are encountered. Uremia occasionally terminates acute nephritis. In most instances however, recovery occurs, or the disease progresses to the sub-acute or chronic form. Neither the intensity of the acute attack nor the degree of nitrogen retention offers a reliable guide to prognosis.

CHRONIC GLOMERULO-NEPHRITIS

The histopathology varies according to the stage of the disease, but in general the picture is one of a healing or a healed inflammatory lesion of the glomeruli. Many of the latter show occlusion and hyaline degeneration of some or of all their

capillary loops; others are replaced by fibrous tissue, and yet others may show compensatory hypertrophy. Proliferation of the cells of Bowman's capsule is often a prominent feature. Sooner or later the tubules are the seat of hyaline or fatty changes; their epithelium becomes flattened and their lumina dilated. Some tubules may show attempts at regeneration, masses of newly formed epithelial cells appearing here and there. Glomerular regeneration is never seen. Sclerosis of arterioles and hypertrophy of their muscular coats are found in the later stages and are probably the result of the sustained hypertension which is such a common feature of the disease. Some vessels may show obliteration of their lumina as a result of active proliferation of their lining cells (endarteritis obliterans). In the following table is given a summary of the characteristic clinical features of chronic glomerulo-nephritis. Compare with table on page 401.

(a) *Albuminuria*, usually not excessive (from 2 to 10 grams per day). Albumin-globulin ratio between 3 and 10 (p. 405). Epithelial, blood, hyaline and granular casts

(b) *Renal insufficiency* (see p. 402); reduced ammonia production and consequent fall in the ammonia-acid ratio; *acidosis*

(c) *Edema* is often absent; when present it is not so prominent a feature as in nephrosis. Reduction of plasma protein and chloride retention are also less pronounced than in nephrosis.

(d) *Hypertension, cardiac hypertrophy and retinal changes* (see p. 128).

(e) Large urine volume (*polyuria*) in earlier stages, *nycturia*; reduced volume (*oliguria*) in later stages; urine of low specific gravity, tending to become fixed around that of deproteinized plasma (1.009 to 1.011). There may be *glycosuria*.

(f) *Anemia*.

(g) *Uremia* usual cause of death.

Kidney disease showing the foregoing features is sometimes spoken of as the *azotemic type*, after the clinical classification introduced by continental authorities.

Though the disease under discussion is primarily a glomerulitis, it will be recalled that the blood supply of the tubules is dependent almost solely upon the glomerular capillaries. At first only a proportion of the capillary loops in a given tuft may be involved in the inflammatory process. The total available filtering surface will be reduced thereby, but the tubules may still be adequately supplied with blood through pervious capillaries. Later, when the glomerular flow becomes greatly

curtailed, the tubules of that nephron undergo degeneration and atrophy. This is the reason, no doubt, that the concentrating function of the kidney (re-absorption of water) becomes impaired in glomerulo-nephritis. The reduced ammonia production, as well as the glycosuria and the fall in the serum calcium which sometimes occur in the disease can also be attributed to tubular involvement; the excretion of sugar and of calcium shows a striking increase (reduced re-absorption) when the tubules are poisoned by uranium in experimental animals.

In some instances, chronic glomerulo-nephritis during its earlier stages shows signs and symptoms almost identical with those of chronic lipoid nephrosis (p. 401), nitrogen retention, hypertension, etc., not appearing until later in the course of the disease. It is then referred to as the *nephrotic type of glomerulo-nephritis*. Edema is a prominent feature. In such cases, apparently, the action of the toxin at first has been upon the tubules which undergo degenerative changes, the effect upon the glomeruli at this time being relatively mild.

NEPHROSIS

(Synonyms: *tubular nephritis, degenerative Bright's disease, parenchymatous nephritis*)

This term embraces those several diseases of the kidney, acute, subacute or chronic, mild or severe, in which the predominant lesion is a *degenerative* one, implicating the *tubular epithelium*. Whereas the toxin of scarlet fever, for instance, acts primarily as a glomerular poison, several other toxic substances act chiefly in causing nephrosis. In many fevers albuminous degeneration (cloudy swelling) of the tubular epithelium occurs, and albumin appears in the urine but disappears after the fever has subsided. This is referred to as *febrile nephrosis*. Degenerative changes (albuminous, fatty) of varying degrees of intensity occur in *diabetes, malaria, pernicious anemia, pregnancy, obstructive jaundice, intestinal obstruction*, etc. *Chemical poisons*, e.g., salts of mercury, chromium, bismuth, uranium, lead and arsenic, methyl alcohol, carbolic acid, etc., may produce mild or severe degenerative changes in the tubules. *Amyloid nephrosis*; in pulmonary tuberculosis chronic pyogenic infections (e.g., osteomyelitis) the tubules show amyloid degeneration and atrophy. Many of the glomerular tufts may also be obliterated by amyloid deposits. The renal arterioles may show similar changes. Not only

lyloid nephrosis, but in some of the other more severe forms, e.g., those due to chemical poisons, the glomeruli may be involved in the degenerative changes, though usually to a much less degree than the tubules.

The clinical manifestations of the different types of nephrosis vary widely. Many are of mild degree and of a temporary nature; a small amount of albumin and a few casts are present in the urine and renal insufficiency is absent. The more severe and chronic forms are as a class characterized by *edema, a high degree of albuminuria, reduction of plasma protein (mainly of the albumin fraction) lipemia and hypercholesterolemia and the absence of hypertension and renal changes*. Except in very severe acute types, such as those caused by chemical poisons in which necrosis of the tubular epithelium may occur accompanied by anuria, renal insufficiency is absent or of moderate degree.

LIPOID NEPHROSIS

(Synonym: *genuine or pure nephrosis*)

This is an exceedingly rare disease, and did it not possess certain features of great clinical and physiological interest its description in a book of this nature would scarcely be justified. The cause of this condition is obscure, though in a certain proportion of cases syphilis appears to predispose to it. The histopathology is one of a pure degenerative disease of the tubular epithelium. The glomeruli are usually normal in appearance, as are also the arterioles and larger vessels. The degenerative change consists of the deposition of anisotropic lipoid material (cholesterol esters) in the tubular cells and interstitial tissue. Cloudy swelling, necrosis or calcification of the epithelium are less characteristic changes. The clinical features are chiefly those given above as characteristic of the chronic nephroses.

- 1) *Edema*, frequently massive with *ascites*, protein content of edema fluid low (0.1 per cent). Low plasma albumin (less than 2.5 per cent) and total protein (less than 5 per cent).
- 2) *Albuminuria*, often excessive (5 to 20 grams or more daily); albumin-globulin ratio in urine high (1 to 20) and low in plasma (see p. 406).
- 3) *Urine* of small volume, of normal or high specific gravity and low in chlorides when edema is present. During recession of the edema the urine volume increases, the specific gravity falls and the chloride excretion rises. Hematuria is absent.
- 4) Absence of hypertension, cardiac hypertrophy and retinal changes.
- 5) *Lipemia* and *hypercholesterolemia* (up to 1000 mg. or more per 100 cc.); lipoid droplets in the urine.

(6) *Low metabolic rate*.

(7) *Absence of renal insufficiency*; uremia does not occur; death usually results from some intercurrent infection, especially peritonitis (pneumococcal).

The cause of the disease is unknown. Two views are held: (a) that it is primarily a degenerative disease of the renal tubules resulting from an unknown toxin; (b) that it is a general metabolic disease of which renal manifestations are merely a part. Epstein believes that the protein in the urine differs from the normal plasma protein, being excreted as any "foreign" protein would be. Several observers have reported differences between the serum proteins of nephrotic patients and those of normal persons. The albumin fraction of the serum in nephrosis was found by Tuchman and Sobotka to contain more tyrosine than normal and the globulin less; and Alving and Mirsky obtained from nephrotic serum an albumin fraction with a cystine content below that in normal serum albumin. The albumin of the protein excreted in the urine was found to contain more cystine than did the corresponding serum protein, but less than that present in normal serum albumin. Bourdillon found from osmotic pressure determinations that the serum proteins of patients with nephrosis had molecular weights from 50 to 100 per cent greater than the normal, whereas, the urinary proteins were lighter than those of normal serum. The molecular weights as determined will of course be average values and Bourdillon offers the explanation that the molecules are of variable sizes, some much larger and others smaller than those of normal serum proteins, and that the glomerular membrane is permeable to the latter but not to the former.

ARTERIOSCLEROTIC KIDNEY DISEASE

(Synonym: *nephrosclerosis*)

This occurs in three forms. (1) In elderly persons the *larger renal arteries*—arcuate, interlobular or interlobar—are chiefly involved in sclerotic changes as part of a general systemic arteriosclerosis. As a result of closure of some of these branches the blood supply may be shut off from relatively large renal areas (infarction). The nephrons within these areas atrophy and the reserve of the kidney becomes reduced. This is a picture of the *senile kidney*. The changes as a rule give rise to nothing more than a mild degree of renal insufficiency. The condition is of no great clinical or physiological interest.

(2) The *renal arterioles* become sclerosed (proliferation of their endothelial cells and a thickening of their muscular coats) as a sequel to *essential hypertension*.

The persistent high pressure is looked upon as the direct cause of the arteriolar changes. The closure of numbers of afferent vessels causes a wide-spread destruction of glomerular tufts which become hyalinized or replaced by fibrous tissue. Degenerative changes occur in the tubules and the interstitial tissue is increased. Renal insufficiency results. When renal symptoms supervene they resemble those of chronic glomerulo-nephritis, but tend to be overshadowed by the primary cardiovascular features. The following are the main differences between this type and glomerulo-nephritis.

(a) Renal insufficiency is not, as a rule, a prominent feature until congestive heart failure supervenes.

(b) Albuminuria slight, absent or intermittent.

(c) Edema a less pronounced feature and usually of cardiac origin.

(d) Greater degree of hypertension and cardiac hypertrophy.

(e) Death usually due to cardiac failure or cerebral hemorrhage.

(3) As a result of *malignant hypertension* (p. 136) the renal arteriolar disease is more intense. Endarteritis and necrosis of the afferent vessels (*malignant nephrosclerosis*) cause a more rapidly progressive destruction of the glomerular tufts. Renal insufficiency develops acutely.

THE PATHOLOGICAL PHYSIOLOGY OF SOME OF THE MAIN FEATURES OF RENAL DISEASE

I. RENAL INSUFFICIENCY

Renal insufficiency means a reduced capacity of the kidney to carry out its functions, namely;—

(a) *The excretion of non-protein nitrogenous substances*—urea, uric acid, creatinine, etc. The rate of excretion of urea is directly proportional to (i) its concentration in the blood when the urine volume is above a certain limit—*augmentation limit* (p. 404). Consequently, when the rate of excretion of urea tends to fall as a result of kidney damage, its concentration in the blood rises and the excretion becomes established at a higher level, (ii) the square root of the urine volume when this is below the augmentation limit, and (iii) the amount of active renal tissue when this is less than about 50 per cent of the normal.

(b) *The excretion of water*. Though there may be polyuria (p. 408) which might suggest that there is no incapacity of the kidney to eliminate water, it will be found that the inefficient kidney cannot respond promptly when an extra demand is made upon this function. Consequently, when a large quantity of water is drunk it is not excreted within the normal time. Furthermore, the specific gravity of the urine does not fall to the low level (1.001 to 1.003) of urine formed in health under the same circumstances, but remains around that of

deproteinized plasma (glomerular filtrate), namely, 1.009 to 1.010.

(c) *Concentrating power* (re-absorption of water) is impaired. The low threshold substances, such as urea, uric acid, etc., are in lower concentration in nephritic than in normal urine even when the concentrating power of the kidney is encouraged by reducing the fluid intake. If fluids are withheld for some time from a healthy person, he passes urine of a high specific gravity, 1.030 or over. The severely impaired kidney is unable to raise the specific gravity much, if at all, above that of protein-free plasma. Taking the two last mentioned functions, (b) and (c), together it may be said that as the renal injury progresses, the specific gravity of the urine after the ingestion of a quantity of water tends to be depressed less and less toward the normal figure of about 1.002; when fluid is withheld the specific gravity is raised with increasing difficulty toward the normal maximum of about 1.030. In other words, instead of showing the great swings in specific gravity of normal urine under varying conditions of fluid intake, nephritic urine tends to become fixed at a specific gravity around 1.010. *Hyposthenuria* is the term used to denote sub-normal concentrating power. *Isothenuria* is a term which means that the kidney cannot form urine with a higher or lower specific gravity than that of protein-free plasma.

When one speaks of renal insufficiency it is the impairment in the functions referred to in the foregoing paragraphs that is meant, since it is for the measurement of the degree of impairment of these functions that the most reliable methods have been devised. Yet, it should be remembered that renal disease does not single out any particular function for attack; when one is impaired others also suffer more or less. *Nitrogen excretion, water elimination, concentrating power, ammonia and hippuric acid production, and base conservation* (p. 392) are all interfered with more or less together. There is one apparent exception; the leakage into the urine of serum protein—proteinuria—which is an indication of some abnormality of the glomerular membrane, may be present in the absence of other signs of disturbed renal function (see *lipoid nephrosis* and *benign albuminuria*). Proteinuria, therefore, though a fault in renal function is not a criterion of renal insufficiency in the ordinarily accepted sense of this term.

Renal insufficiency may be *relative*, as when there is an accumulation of nitrogenous products in the blood, and water elimination is difficult

protein diet which will encourage the regeneration of plasma protein would appear, therefore, to be a rational procedure in the treatment of nephrotic edema. It also follows that it is undesirable to remove large quantities of edema, or ascitic fluid mechanically (paracentesis) for, though the protein content of the fluid is very low, the total amount lost to the body through such a procedure may be significant.

The question of water and salt retention

It was thought at one time that edema was due to the inability of the kidney to excrete water and salt. The blood volume was believed to increase as a result of the water retention. Increase in the blood water (hydremia) was also encouraged, apparently, by the retention of salt, since the accumulation of water would tend to restore the normal osmotic pressure of the body fluids. Recent work has shown that in lipoid nephrosis, in which edema is a prominent feature, the kidneys have no difficulty in excreting water or chloride, for though the urine is of small volume and low in chloride while the edema is forming, when this subsides after treatment, large quantities of water and salt are eliminated. Even in the nephrotic type of glomerulo-nephritis, though there is impaired water excretion, this is not the primary cause of the edema, and the ability of the kidney to excrete chloride is little if at all reduced; the sodium chloride of the blood may be normal or even below normal and sodium chloride injected intravenously actually disappears from the blood of the nephritic subject more quickly than from the blood of a normal person. On the other hand, when the excretion of water and salt is entirely prevented, as during suppression of urine, the blood chloride rises yet edema does not necessarily occur. Direct estimations indicate that the plasma volume in nephrotic edema is not increased but in some instances is actually reduced.

Nevertheless, there can be no doubt that salt retention is an important factor in the production of edema. For example, the administration of sodium chloride to the patient on the verge of edema precipitates the condition; the edema disappears again upon a salt-free diet. Sodium bicarbonate has a similar effect, while chlorides other than sodium chloride (e.g., KCl, NH_4Cl) either exert no effect or through their acidifying effect (pp. 18 and 388) cause diuresis and the discharge of the edema fluid. It has also been shown by Hastings and Van Dyke that edema can be produced in dogs by the administration of

sodium bromide. These and other facts have suggested that the influence upon the production of edema is exerted by the sodium rather than by the chloride ion.

The retention of salt and water in nephrosis is apparently due to extrarenal factors. It is evident, that since the water and sodium chloride of the blood are not increased the kidney need not be held responsible for their retention in the body. The present day view is that the water and salt are deviated into the tissues and do not reach the kidney for excretion—a conception expressed in the term *pre-renal deviation*. An explanation for the influence of salt in the formation of edema fluid is suggested by the following observations upon normal persons. (a) When sodium chloride is given in excess it does not immediately appear in the urine, there being a lag of three days or so in its excretion. (b) It has been shown by Padtberg that the skin and subcutaneous tissues store the ingested chloride. (c) Veil found that when a large amount of sodium chloride was given, a rise in blood sodium chloride and a great increase in blood water first occurred. Later, the water and salt were poured into the tissues, and the composition of the blood returned to normal. Finally, the salt was excreted, though no apparent change in the blood chloride occurred. (d) Edema may be produced in healthy persons by the administration of very large quantities of salt followed by the drinking of an abundance of water. Baird and Haldane took sodium chloride (38 grams) or sodium chloride and bicarbonate in 500 cc. of water. If, while the diuresis which followed the salt ingestion was subsiding, $2\frac{1}{2}$ liters of water were drunk, there was no apparent effect, the urine volume continuing to fall. Edema about the ankles was noted. When, however, an additional 500 cc. were drunk, profuse diuresis resulted. It was also found that water or isotonic saline caused a much greater diuresis than hypertonic saline. They give as the probable explanation of their results that the salt was first deposited as a hypertonic solution in the tissues, the water which was ingested later left the capillaries to produce an isotonic tissue fluid. Water ingested in excess of this requirement was excreted. The smaller diuretic effect, i.e., the greater water retention, of hypertonic saline as compared with that induced by water or hypotonic saline finds a similar explanation. (See also water diuresis, p. 389.)

It is seen, therefore, that even in health the balance between intra- and extra- capillary fluid

can be upset and a temporary edema produced. Normally fluid is forced out of the capillary near the arterial end where the blood pressure overbalances the colloid osmotic pressure (p. 23). At the venous end, where the blood pressure no longer exceeds the pressure of the tissue fluid and the osmotic pressure of the plasma proteins, water is taken up. The fluid poured into the tissues as a result of the deposition of chloride, therefore, soon undergoes reabsorption. When, however, the concentration of plasma protein is low, reabsorption becomes more difficult. The water which has migrated from the vessels to dilute the tissue fluids to isotonicity is not readily removed. Deficit in the plasma protein is therefore the primary cause of nephrotic edema; salt retention in the tissues is a contributory factor; salt, like water itself plays a passive rôle simply enabling more isotonic tissue fluid to be formed i.e., providing

TABLE 31

Rate of excretion of casts, blood and epithelial cells
per twelve hour period
(After Addis)

	AVERAGE	LOWEST	HIGHEST
Casts.....	1,040	0	4,270
Red blood cells.....	65,750	0	425,000
White blood and epithelial cells.....	322,500	32,400	1,835,000

one of the essential constituents of the edema fluid. In other words, water can only be retained as an isotonic fluid; if, therefore, salt is withheld the excess water is excreted. It is also recognized that in certain dehydrated states ingested water is not retained unless salt is also supplied.

In *acute nephritis*, especially in the earlier stages, edema may occur in the absence of plasma protein deficit. The edema is not widespread as a rule, but may appear before the renal manifestations. It is considered as due to increased permeability of the capillary wall; the high protein content of the edema fluid (1 per cent) supports this conclusion. It is likely that the toxic substance which has produced the inflammatory lesions in the glomerular capillaries has also injured the systemic vessels. It is significant that poisons, such as the toxins of diphtheria and scarlet fever, and other substances which cause glomerular damage, are also general capillary poisons.

IV. CASTS

Part of the protein material which has passed through the glomerulus may become moulded in the tubules to

form the microscopical urinary bodies known as casts. Blood which has exuded from the glomeruli, epithelial cells shed from the tubules, or lipoid material, may become moulded in a similar way. The several varieties of casts—*blood*, *epithelial*, *fatty* or *waxy*—are named according to the material of which they are composed. *Hyaline* casts are formed of coagulated albumin and are translucent and homogeneous. *Granular* casts are made of a conglomerate of blood or epithelial cells in a matrix of albumin. In the terminal stages of renal failure the shed epithelial cells of the larger collecting tubules form exceptionally large elements termed *renal failure casts* (Addis). The urine may also contain many free red and white cells, the numbers varying according to the type and severity of the kidney lesion. Nevertheless, the presence in the urine of relatively small numbers of hyaline casts or even of a few blood cells is by no means an indication of renal disease. Addis examined the urine of 74 healthy medical students and found hyaline casts in 45. The figures for the rates of excretion for the entire group are given in table 31.

V. POLYURIA AND OLIGURIA

An increase in the volume of the night urine—*nycturia*⁴ (p. 396)—is often one of the first indications of chronic renal disease, and polyuria during day and night is characteristic of the earlier stages of chronic glomerulo-nephritis. Unlike that of diabetes insipidus, the polyuria of kidney disease does not respond to pituitrin. Nycturia is usually defined as the passage during the night period of over 500 cc. of urine having a specific gravity of less than 1.018. It is looked upon as the effort of an inefficient kidney to catch up with the work of excreting urea and other low threshold substances which it has been unable to accomplish during the day. In the later stages of renal insufficiency the output of urine during the 24 hours is reduced considerably below the normal—*oliguria*.

The polyuria of chronic nephritis is usually considered to be a compensatory response of the kidney to the reduction in the number of functioning renal units. Certain experimental observations seem to support this conception.

Rose Bradford found that when a part—sometimes as small as one-eighth or one-fourth—of the renal substance of an animal was excised the remaining tissue responded within 24 hours by excreting large quantities of very dilute urine. The polyuria persisted through-

⁴ This applies, of course, only under ordinary conditions of fluid intake. A healthy person may have to get up in the night to pass urine if he has drunk much fluid before retiring.

out the period of observation, which extended over a period of from 1 to 2 years. When the amount of excised renal tissue was small, urea retention did not result. Verney and his associates carried out similar experiments upon isolated kidneys perfused by means of a heart-lung preparation. When a primary branch of the renal artery of one kidney was ligated 50 per cent of its tissue was put out of action. Nevertheless, though the blood flow was reduced by one-half, there was no reduction in the quantity of urine formed by this kidney. It produced as much urine as the sound kidney of the opposite side. In other words, the active kidney tissue which remained, immediately doubled its output and compensated fully for the functionless portion. The urine flow gradually increased throughout the experiment until finally it was some 30 times greater than that of the sound kidney. The composition of the urine from the injured kidney was altered. The urea percentage as well as the total quantity excreted showed a profound fall. It appears, however, that per unit of functioning tissue, the affected kidney excreted slightly more urea than the normal one. The chloride percentage was unchanged, so that the absolute amount, i.e., the amount per unit of time, excreted by the functioning half of the kidney was much greater (4 times in one experiment) than that excreted by the kidney before ligation, or than that excreted by the kidney of the opposite side. The specific gravity of the urine approached that of deproteinized plasma. In brief, the injured kidney excreted much more water and chloride and much less urea than the normal organ. The results of these experiments resemble closely those of chronic nephritis.

The polyuria in the foregoing experiments has been ascribed to the greater quantity of filtrate formed as the result of adaptive vascular changes within the kidney. The latter are probably brought about through a local nervous mechanism but the possibility of an intrarenal hormonal factor being concerned must also be considered. The juxta-glomerular apparatus (p. 379) is the most likely structure through which the control of the intrarenal circulation is effected. Another factor in the augmentation of the urine flow in Verney's experiments is, as pointed out by Winton, the reduction in intrarenal pressure (p. 382) resulting from the diminished blood supply. In other words, the kidney shrinks within its capsule, the pressure of the renal tissue upon the tubules being thus relieved and the effective filtration pressure increased. The polyuria of chronic nephritis also is probably due in part to an increased filtration brought about in the following ways. (a) By changes in the relative calibers of the afferent and efferent vessels (p. 387). (b) By a rise in general blood pressure (see p. 381).

This is a variable and apparently a non-essential factor, for polyuria may be present without any rise in systemic blood pressure and we have just seen that it occurs in the isolated kidney. (c) The reduction in the plasma osmotic pressure resulting from protein deficit will also serve to augment the *effective* filtration pressure. The absence of a rise in blood pressure in some cases of chronic nephritis with polyuria may find an explanation in the fact that the plasma osmotic pressure has been greatly reduced (p. 381).

The polyuria of nephritis, however, is not largely, at any rate, a compensatory response, but is also largely due to tubular impairment. It can readily be understood how failure of tubular function would, through diminishing re-absorption, increase the urine volume, even though the glomerular filtrate were of normal composition. But when the filtrate has a high urea content and consequently a higher osmotic pressure than normal, the damaged tubules, in order to absorb the same quantity of fluid (p. 388), would actually be required to perform more work than in health. Even in the experiments on the isolated kidney, the fact that the quantity of urea excreted by the reduced kidney was, per unit of functioning tissue, only slightly increased, while the entire quantity excreted by this kidney was greatly diminished, indicates that little benefit actually resulted from the polyuria.

It has already been mentioned (p. 402) that polyuria is no indication that the kidney's ability to excrete water is not greatly impaired, for the increased urine volume may almost correspond to the maximum diuresis of which the kidney is capable.

It should also be pointed out that impairment of re-absorption will, paradoxical as it may seem, finally lead to a reduction in urine volume through its unfavorable effect upon filtration, for failure in the re-absorption of fluid from the tubules raises the pressure within Bowman's capsule and so opposes the pressure of blood within the capillary loops (p. 388). This effect may for a time be countered by issuing further calls upon the vascular mechanisms, already mentioned, to increase the intraglomerular pressure. The progressive destruction of the capillary loops, by reducing the extent of the filtering surface, is of course also a factor in causing the oliguria which occurs in the later stages of the disease. Another possible factor should not be lost sight of, namely, the greater back diffusion which, as Richards

(p. 384) has shown, occurs when the tubular membrane is severely damaged.

VI. UREMIA

Two types of uremia are recognized—*true uremia* and *false or eclamptic uremia*.

True uremia is the terminal manifestation of renal failure. Its chief features are muscular weakness, dyspnea, mental disturbances, increased tendon jerks, nausea and vomiting, muscular twitchings, stupor and finally coma with periodic breathing. The excretion of a small volume of urine of low specific gravity (around 1.010), a high degree of urea retention (150 to 500 mg. or more per 100 cc.) and a low blood urea clearance (below 10 per cent of the normal) precede the uremic state.

Though the symptoms are associated with a high degree of nitrogen retention, none of the known nitrogenous wastes, urea, uric acid or creatinine, is responsible. None of these is toxic in relatively large doses; uremia is not produced when animals are fed these substances and their concentrations in the blood raised well above the limits found in renal insufficiency. Bollman and Mann, experimenting upon dogs, implanted the ureters into the intestine. The continued reabsorption of urine caused a rise in the blood urea nitrogen to over 800 mg. per cent yet no toxic symptoms resulted.

The manifestations of uremia are divisible into two groups, namely, those of *depression*, e.g., apathy, muscular weakness, stupor and coma, and those indicative of *neuromuscular hyperexcitability*, e.g., increased tendon jerks, muscular twitchings or jerkings and other irritative phenomena. Sometimes one type of symptom predominates, sometimes the other. The diverse nature of the manifestations strongly suggests that they are due not to a single retention product but perhaps to several. Becker's studies provide important evidence for the view that the signs of depression are due to the absorption of putrefactive products, especially phenols, from the intestinal tract. The hepatic functions are defective in the uremic state and failure of the detoxicating function of the liver (p. 507) combined with renal insufficiency will permit the accumulation in the circulation of free phenols, as well as of the less toxic conjugated compounds. Becker's observation that phenolic bodies are increased in the blood in uremia has been confirmed by Mason and his associates. Among the most important observa-

tions which can be cited in support of Becker's conception are that symptoms of chronic phenol intoxication closely resemble those of uremia; that the introduction of aromatic amino-acids into the rectum of a uremic patient increases severity of the symptoms. Furthermore, onset of the uremic manifestations coincides with the appearance of phenols in the cerebrospinal fluid.

The most probable cause of the increased neuromuscular excitability is a reduction in concentration of ionized calcium (p. 704) in body fluids and tissues, which is most likely in turn the result of phosphate retention. It is possible on the other hand, that an increase in organic metabolites such as citrate or oxalate may also result in the depression of the ionized calcium. There is some evidence that the irritative phenomena are in part due to guanidine intoxication. It will be recalled that the guanidine nucleus contained in the creatinine molecule and that creatinine retention is a prominent feature of chronic nephritis.

False or eclamptic uremia is characterized by epileptiform convulsions which are due, apparently, to cerebral edema. This type may occur in the absence of renal insufficiency (as in nephroses), indeed, it may occur in the absence of renal disease. It is occasionally seen in angioneurotic edema (p. 32) which supports the belief in its being due to cerebral edema. Other signs of increased intracranial pressure, e.g., severe headache, vomiting, slow pulse, hypertension and sometimes choked optic discs, are present. Volhard regards cerebral edema as due in many instances to intracranial circulatory disturbances—arteriolar constriction with consequent asphyxia and increased permeability of the walls of the cerebral capillaries.

A type of false uremia resembling the foregoing in several respects occurs in arterial hypertension. It is thought to be due to intracranial vascular disturbances alone, i.e., without cerebral edema. Epileptiform convulsions, headache, vertigo, homonymous hemianopia, hallucinations, aphasia, temporary paralysis, paroxysmal attacks of dyspnea, or even Cheyne-Stokes breathing, may occur. *Periodic encephalopathy* is a term sometimes employed in referring to this condition.

VII. ACIDOSIS

Acidosis is frequently present in the later stages of chronic glomerulonephritis. This is not surprising, since the insufficiency of the kid-

involves all its functions, and one of the most important of these is the regulation of the acid-base balance of the plasma. The fall in the ammonia/acid ratio found in nephritic conditions (p. 393) indicates a reduction in ammonia production. Acids must then be excreted to a greater extent in combination with fixed base which is therefore lost to the body. The conversion of the alkaline phosphate to the acid salt occurs in the distal tubules, and it is not improbable that impairment of this function is also responsible for a loss of base. Peters and his associates have found a reduction in bicarbonate reserve in a large proportion of non-edematous nephritic cases. The diminished alkali reserve was found to be chiefly due to reduction in total base. Contributory causes were the accumulation of phosphates and sulphates and, when carbohydrate of the diet was deficient, of ketones.

VIII. ARTERIAL HYPERTENSION (SEE P. 128)

MICTURITION

Outline of the anatomy of the urinary tract

The muscular coat of the *ureter* is arranged in three layers, an *external longitudinal*, a *middle circular* and an *internal longitudinal*.

The muscle of the *urinary bladder* is also disposed in three layers, an *external*, a *middle* and an *internal*. The fibers of the external layer run longitudinally, that is, in the long axis of the bladder. The fibers of the middle layer are thinly scattered; they have a circular arrangement and run both transversely and obliquely to the long axis of the viscus. The fibers of the internal layer follow a reticular pattern but for the most part run longitudinally.

The vesical mucous membrane is separated from the internal muscular layer by a submucous coat of loose areolar tissue. The mucosa is thin and, when the bladder is empty or contains only a small quantity of urine, has a corrugated appearance due to the presence of numerous folds or *rugae*. The latter disappear when the bladder becomes distended by the accumulation of urine. The vesical epithelium as well as that lining the ureter is of the type called transitional. The mucosa of the empty bladder shows several layers of cells; those of the deepest layer are cuboidal or even columnar in shape; the most superficial layer consists of broad cells with a convex free surface. In the mucosa of the distended bladder only two cell layers are evident, a deep stratum of cuboidal and a superficial one of large squamous cells.

The *peritoneum* covers the superior surface of the bladder only.

The ureters pierce the wall of the fundus (or base) of the bladder very obliquely. From a half to three

quarters of an inch of their lower ends are embedded in the vesical muscle. During contraction of the wall of the bladder these portions of the ureters are compressed by the muscle fibers, thus preventing the reflux of urine as the intravesical pressure rises. The urethral orifice which is situated at the most dependent part of the bladder is guarded by the *vesical sphincter* (*internal sphincter*). This is formed by the condensation of the muscle fibers of the circular layer. The triangular area marked out by the urethral orifice and the two ureteral orifices is called the *trigone* (*trigonum vesicae*). The muscle of the bladder wall is referred to as the *detrusor urinae*. The male urethra is embraced in its membranous portion by the *sphincter urethrae membranaceus*, a striated muscle which is frequently referred to as the *external sphincter*. The *bulbocavernosus* muscle, which is applied to the urethral bulb and surrounds the corpora cavernosa penis, also exerts a constrictor action upon the urethra. The urethral wall itself contains two layers of smooth muscle, an outer circular and an inner longitudinal; in women (who do not possess an external sphincter of striated muscle) this serves to prevent the escape of urine after paralysis of the internal sphincter. The epithelial lining of the urethra is of the columnar type except near the bladder where it is of the transitional variety, and a short distance from the external urethral orifice where it is stratified and squamous.

FILLING OF THE BLADDER

The ureters exhibit rhythmical peristaltic contractions which travel at a speed of from 20 to 25 mm. per second (rabbit) and at a frequency from 1 to 5 per minute, according to the volume of urine formed by the kidney. The peristaltic waves serve to propel the urine from the pelvis of the kidney to the bladder. The urine therefore enters the bladder not in a continuous stream but in separate squirts synchronous with the arrival of the peristaltic waves.

The detrusor muscle exhibits two types of activity, a sustained contraction or tonus, and intermittent contractions.

The bladder, in common with other hollow viscera, is capable of adjusting its tone and so of adapting its capacity to changes in the volume of its contents with relatively little alteration in internal pressure. It thus differs in its behavior from an elastic hollow sphere composed of a non-living material. For example, when a moderate quantity of fluid is run into the bladder through a catheter the intravesical pressure shows a transient rise, due to the tonic resistance offered by the bladder wall, but then declines again to near its previous level as adaptation occurs. As successive volumes of fluid are introduced the

curve of intravesical pressure therefore shows a gradual step-like ascent until the bladder contents are unusually large. From then on further additions of fluid cause a much more abrupt rise in pressure. The adaptation is not to a constant pressure (15 cm. of water), as was previously taught, but is always to a pressure a little higher than that existing before the fluid was introduced. In the experiments of Denny-Brown and Robertson upon normal human subjects fluid was run into the bladder 50 cc. at a time. An increase in volume of the contents of the bladder from 50 cc. to 400 cc. caused little change in pressure (fig. 179). When completely paralyzed (as during the first two or three weeks following a transverse lesion of the cord) the bladder does not behave in this way, but simply as an inert elastic bag showing no tendency to respond to an increase in tension upon its walls or to adapt itself to its contents (Holmes); when successive quantities of fluid are introduced the curve of intravesical pressure rises along a perfectly smooth line.

Tension is the adequate stimulus for the sensory end organs in the bladder wall. When therefore the bladder becomes distended by the accumulation of urine and the intravesical pressure reaches a certain value, rhythmical contractions of the detrusor muscle are set up. As the pressure rises further these culminate in the movements constituting the micturition reflex, namely, a strong contraction of the detrusor muscle accompanied by relaxation of the internal sphincter, and followed by opening of the external sphincter. It is usually stated that the reflex occurs at an intravesical pressure of from 15 to 18 cm. of water, but it may be activated by a pressure considerably lower than this. The urine is expelled with considerable force, the pressure within the bladder rising during the contraction of the detrusor to around 130 cm. of water. Since adaptation requires a certain time to take place, the reflex is activated at a lower urine volume than usual if the accumulation of urine is rapid. At the average rate at which urine forms micturition occurs, unless restrained, after from 250 to 300 cc. have collected.

THE VOLUNTARY CONTROL OF MICTURITION

The act of micturition though essentially reflex in nature is usually initiated by an effort of the will; it also can be voluntarily inhibited or be interrupted at any stage. The desire to urinate is accompanied by a vague feeling in the penis or perineum. The sensation appears when the urine

volume is from 200 to 300 cc. If the act is long postponed a feeling of fullness and discomfort culminating in pain results. It is only in the infant or when, as a result of disease, the bladder is isolated from the control of the higher nervous centers, that micturition is a purely reflex act. Under ordinary circumstances in the adult, when the desire to micturate arises, the act is restrained until an opportunity for emptying the bladder presents itself. The restraint is then lifted and the reflex occurs automatically.

The voluntary restraint exerted upon micturition consists, according to Denny-Brown and Robertson, of inhibition of the detrusor with contraction of the external sphincter and perineal muscles. No evidence was obtained by these observers that the internal sphincter was under direct voluntary control, though a reciprocal increase in tone of the sphincter muscle accompanies inhibition of the detrusor. It was found that at a certain urine volume, contractions of the bladder and a consequent rise in intravesical pressure could be readily induced by an effort of the will; contraction of the abdominal muscles was not necessarily associated with the performance of the act. The removal of restraint and the voluntary facilitation of the spontaneous bladder contractions are considered to be the important factors. At low urine volumes restraint is apparently exercised subconsciously. These observers therefore regard the act of micturition as being normally controlled through variations in voluntary and subconscious restraint of the reflex mechanism. Micturition therefore presents a very unusual feature in that movements innervated by autonomic nerves can be controlled by voluntary impulses.

Though the abdominal muscles play a non-essential part in micturition, the act, under ordinary circumstances, is started by the contraction of these muscles; and it is well known that the bladder can be emptied though it contains only a few cubic centimeters of urine. The flow of urine is also accelerated during micturition by the rise in intraabdominal pressure induced by the voluntary contraction of the abdominal muscles. Relaxation of the muscles of the perineum occurs as an associated movement at the commencement of micturition; the significance of this movement is obscure. After the bladder has been emptied the bulbocavernosus muscle (ejaculator urinae) contracts and expels urine which had been left in the urethra.

THE REFLEX MECHANISMS OF MICTURITION

Barrington describes six integrated reflexes as constituting the act of micturition in the cat, namely:

(1) *Contraction of the detrusor* evoked by distending the bladder; the afferent and efferent limbs of this reflex are in the pelvic nerves, its center in the hind-brain. Contraction of the detrusor is accompanied by reciprocal relaxation of the internal sphincter.

(2) *Contraction of the detrusor* caused by running fluid through the urethra. The afferent pathway for this reflex is in the pudendal (pudic) nerves, its efferent in the pelvic nerves and its center in the hind-brain. Through this reflex the contraction of the detrusor caused by the first reflex is sustained until the bladder is completely emptied.

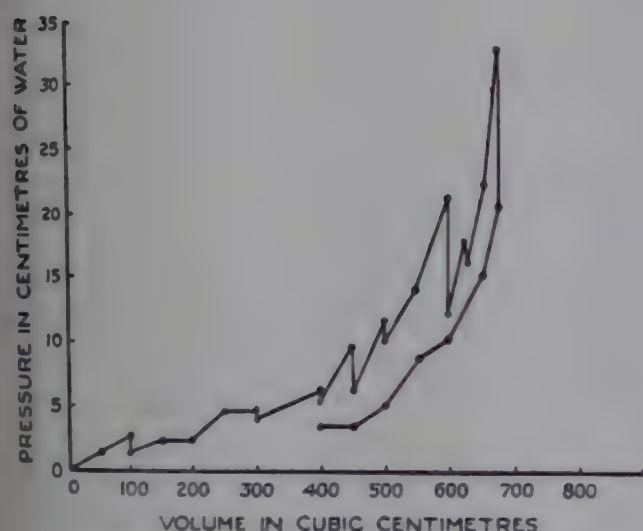


FIG. 179. Curve of pressure changes in the human bladder during filling (upper curve) and emptying (lower curve). (After Denny-Brown and Robertson.)

(3) *Contraction of the detrusor* (transient and weak) when the proximal portion of the urethra is distended. The hypogastric nerves contain both afferent and efferent paths for this reflex; its center is in the sacral part of the cord.

(4) *Relaxation of the external sphincter* when fluid passes along the urethra. Afferent and efferent fibers are in the pudendal (pudic) nerves, the center is in the sacral part of the cord.

(5) *Relaxation of the external sphincter* when the bladder is distended. The afferent path is in the pelvic, the efferent in the pudendal nerves, its center in the sacral part of the cord.

(6) *Relaxation of the plain muscle in the proximal third of the urethra* caused by distending the bladder. Both afferent and efferent paths of the reflex are in the pelvic nerves; its center is in the sacral part of the cord.

In the normal act of micturition the first of these reflexes, namely, contraction of the detrusor in response to distention of the bladder, brings the

others, with the exception of the third automatically into action. It is questionable whether the third reflex is called into play under ordinary circumstances.

THE INNERVATION OF THE URINARY TRACT

The *ureters* in their upper part receive sympathetic fibers from the renal plexus, in their middle part from the spermatic (or ovarian) plexus and near the bladder from the hypogastric nerves. The sympathetic fibers to the ureters exert a predominantly motor effect, though it appears that inhibitory fibers are also derived from the sympathetic. It is thought by some that the

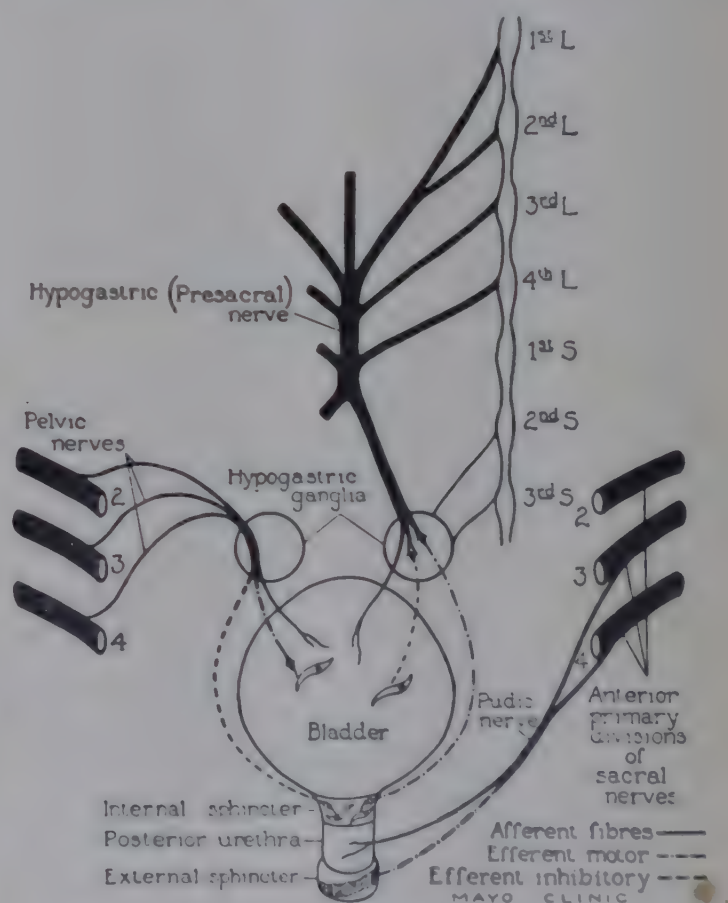


FIG. 180. To show innervation of the bladder. (After Learmonth.)

ureter receives fibers from the parasympathetic as well, since certain parasympathomimetic drugs cause motor effects. The existence of a parasympathetic innervation has not been demonstrated anatomically.

The *efferent nerves to the bladder* are the sympathetic and parasympathetic. The *sympathetic* furnishes inhibitory fibers to the detrusor muscle, and motor fibers to the trigone, internal sphincter and the smooth muscle of the proximal part of the urethra.⁵ These fibers arise from the lumbar

⁵ The sympathetic also causes contraction of the urethral orifices and of the muscle of the seminal vesicles, ejaculatory ducts and prostate.

spinal segments and pass through the inferior mesenteric plexus, the superior hypogastric plexus (presacral nerve) and the inferior hypogastric plexus to reach the hypogastric ganglion (fig. 180). Postganglionic fibers, which probably have their origins in the latter ganglion, enter into the formation of the vesical plexus; this lies in relation to the fundus of the bladder (the hypogastrics in some species apparently contain motor as well as inhibitory fibers).

The *parasympathetic* supplies motor fibers to the detrusor muscle (which govern the tonus and contractile mechanisms) and inhibitory fibers to the internal sphincter. The sympathetic and parasympathetic nerves are therefore reciprocal in their actions. The parasympathetic fibers arise from the second and third sacral spinal segments and to some extent from the first and fourth. They are conveyed in the pelvic (see also p. 942) nerves (*nervi erigentes*) to connect with ganglion cells lying in close relation to the bladder wall. According to Henderson and Roepke, the tonus mechanism is cholinergic (p. 948) but not the phasic contractions.

Both sets of autonomic nerves apparently exert a constant influence upon the tone of the detrusor and internal sphincter; the effect of one set being balanced against the other. Section of the sympathetic or parasympathetic causes, respectively, an increase or decrease in tone of the sphincter. In paresis of the bladder due to injury of the parasympathetic innervation, excision of the presacral nerve is sometimes performed with the object of removing the inhibitory influence of the sympathetic and thus enhancing the action of the pelvic nerves. Voluntary control of the detrusor is exerted apparently through the pelvic nerves.

The striated muscle constituting the external sphincter is innervated through the pudendal (pudic) nerves.

The *afferent* paths from the bladder travel in both pelvic and hypogastric nerves, those from the urethra in the pudendal nerves. The afferent fibers essential for the reflex movements of the bladder are contained in the pelvic nerves, those for the movements of the urethra in the pudendals. The hypogastric nerves contain no afferents for any of the important reflex mechanisms. The sensations set up by distension of the bladder are conveyed in both the pelvic and hypogastric nerves. The sensation of pain travels chiefly in the hypogastrics, but also in the pelvic nerves. Excision of the presacral nerve is practised for the

relief of vesical pain. Tactile and thermal sensations are conveyed from the bladder mainly in the pelvic nerves (Learmonth).

THE NERVE CENTERS GOVERNING MICTURITION

Centers for micturition are situated in the mid-brain, hind-brain and spinal cord. The observations cited on page 412 upon the voluntary control of the detrusor muscle also indicate the existence of a center at the cortical level, and electrical excitation of the premotor area causes a rise in vesicle pressure followed by micturition. Increase in the tone of the bladder wall follows electrical stimulation of the anterior hypothalamic nuclei; stimulation of the posterior nuclei causes inhibition (Beatty and Kerr).

Barrington, experimenting with cats, found that destruction of a small area of the hind brain (lying ventral to the internal edge of the superior cerebellar peduncle and extending forward from the level of the motor nucleus of the fifth nerve to the anterior end of the hind-brain) temporarily abolished the animal's ability to empty its bladder voluntarily. Destruction of an area in the mid-brain, extending from the ventral part of the posterior end of the cerebral aqueduct to just beyond the mesencephalic root of the fifth nerve, was followed by permanent loss of voluntary micturition.

The reflex performance of the act was not, however, impaired. A more extensive lesion in the region of the mesencephalic root caused, in addition, frequency of micturition. Levin and Longworth observed that, in cats, injury to the tegmentum of the mid-brain was followed immediately by hyperactivity of the detrusor muscle to stretch. The capacity of the bladder becomes reduced as a consequence and rhythmic waves of contraction appear. After a time, this increased activity diminishes and the bladder enlarges again.

The spinal centers lie in the second, third and fourth sacral segments. Only the third, fourth, fifth and sixth reflexes described on page 413 are carried out through the spinal centers.

The descending and ascending paths conveying impulses to and from the spinal centers of micturition are situated in the dorsal half of the lateral column of the cord near its periphery, i.e., in close proximity to the pyramidal tract. The fibers of these paths show extensive crossing in the sacral segments (Barrington).

THE EFFECTS OF NERVE SECTION AND OF CORD INJURIES UPON MICTURITION

Section of the hypogastric nerves does not interfere with micturition; these nerves contain neither efferent

nor afferent fibers essential for the performance of the act. Incontinence which might be expected to result (since motor fibers are conveyed by this nerve to the internal sphincter) does not occur. Indeed, incontinence does not follow a prostatectomy operation involving destruction of the internal sphincter, for the external sphincter is capable alone of preventing the escape of urine. Frequency of micturition was found by Barrington to follow section of the hypogastrics in the cat; it also occurs as a temporary effect of resection of the presacral nerve in the human subject. The phenomenon is due, apparently, to the loss of the inhibitory action of the sympathetic upon the tone of the detrusor and the impairment of the ability of the bladder to adapt its capacity to as large a volume of urine as usual.

Section of the pudendal nerves in the human subject is also, according to Learmonth, without any notable effect upon micturition, though of course paralysis of the external sphincter results.

Section of the pelvics causes paralysis of the bladder wall. The detrusor is atonic; the tone of the internal sphincter is raised. Retention of urine with overdistension of the bladder and overflow—dribbling—occurs. Barrington found that the tone of the sphincter diminished after a few days and the animal, apparently experiencing the sensation of fullness of the bladder, assumed the usual position for micturition and performed the act by a contraction of its abdominal muscles.

Severance of the posterior sacral nerve roots is followed immediately by the loss of all the important reflexes of micturition since the afferent paths (through the pelvics and pudendals) are interrupted; the bladder wall is flaccid and the resistance at the internal sphincter is increased. However, after a period of overdistension with overflow, the bladder empties itself automatically at intervals. The sensations of vesical distension (afferent fibers of hypogastrics intact) are retained.

Destruction of the sacral nerves (as in lesions of the cauda equina) or of the spinal centers will interrupt not only motor impulses to the bladder, but also the afferent impulses travelling by the pelvics and pudendals. The bladder is then completely isolated from central nervous control; but, after a period of retention of urine with overflow it expels its contents automatically. The detrusor and internal sphincter act coöordinately. Such an action suggests a neural mechanism of some sort. It occurs in animals even after the hypogastrics have been sectioned as well, and time allowed for degeneration to occur; it cannot therefore be due to preganglionic axon reflexes. Probably, in such and other instances in which motor impulses from the central nervous system have been interrupted, local reflex arcs through ganglion cells in the vesical plexus or bladder wall are responsible for the automatic action. The latter is only a makeshift for the normal micturition reflex since the bladder is not completely emptied but always retains a part of its contents (residual urine).

After transection of the cord above the sacral region, normal micturition cannot occur. Nevertheless, after a variable period of retention with overflow the spinal centers assume control and the bladder empties at intervals automatically (see also mass reflex, p. 1470). Owing to the absence of the first and second reflexes of Barrington which, as just mentioned, are governed by higher centers, the bladder does not empty itself completely, but always contains a quantity of residual urine.

Bladder sensibility is completely lost following section of the hypogastrics and pelvic nerves or transection of the cord above the entrance of the afferent fibers of the hypogastrics. Injury or disease (e.g., tabes) of the posterior columns involving these fibers together with those from the sacral roots will have a similar effect.

SECTION V. DIGESTION

CHAPTER XXXVIII

THE SALIVARY GLANDS AND THE SECRETION OF SALIVA

General description and structure of the glands

Saliva is secreted mainly by three paired masses of cells—the *submaxillary*, *sublingual* and *parotid glands*. There are also small glands scattered over the buccal mucous membrane, which secrete a mucoid fluid. The cells of the glandular tissue are aggregated into a great number of small groups, the individuals of which are arranged in a single layer around a small central cavity or alveolus. The cells are more or less wedge-shaped with their apices converging toward the central cavity and their bases directed outwards. The cells pour their secretion into the alveolus from which a fine duct drains the secretion away. Ducts from neighboring alveoli join to form ducts of larger caliber which unite again to form still larger trunks, until finally through a succession of junctions and the formation of channels of ever increasing size, the secretion is emptied into the mouth by a single large duct, in the case of the submaxillary and parotid glands, or by several of medium size, in the case of the sublingual. The general arrangement of the ducts reminds one of the stem branchings of a bunch of grapes—the rounded alveoli at the ends of the finest channels corresponding to the grapes. Glands showing such a pattern are, therefore, termed *racemose*.

There are two types of salivary cells—*serous* and *mucous*. The alveoli of the *parotid gland* are composed entirely of one type—the serous. This type of cell secretes a thin watery fluid. The *submaxillary gland*, on the other hand, in man, is of the mixed type, some of its alveoli are composed entirely, like the parotid, of serous cells, while others contain only cells of the mucous type. The two varieties of alveoli are indiscriminately intermingled with one another, either singly or in clusters. The mucous cells secrete a thick, viscid juice rich in mucin. In the *sublingual*, the alveoli are predominantly of the mucous type though a few serous alveoli may also be seen. In both the submaxillary and sublingual glands, particularly the former, the two types of cells may also be found in a single alveolus. The serous cells then appear as crescent-shaped elements—*demilunes*—pressed against the periphery of the alveolus between the limiting membrane and the larger, more numerous mucous elements (fig. 181).

The *parotid secretion*, as naturally follows from the character of its cells, is thin and watery in nature; it has a low content of organic material. It is delivered into the mouth through the *duct of Stensen*, which

opens upon the inner surface of the cheek opposite the second molar tooth. The duct of the submaxillary—*duct of Wharton*—runs from the substance of the gland which lies under shelter of the mandible, and opens upon the floor of the mouth to one side of the frenum of the tongue. The secretory ducts of the sublingual—the *ducts of Rivinus*—are several fine tubes which open beside the frenum. The secretion from the submaxillary gland may be either thin and watery (serous) or thick and viscid (mucous), the character at any time depending, as shall be shown later, upon the nature of the secretory stimulus. The *sublingual secretion* on account of its scarcity in serous cells is usually of the mucous type.

MINUTE APPEARANCE OF THE SECRETORY CELLS. The cytoplasm of either the serous or mucous cell is not homogeneous but shows a granular structure, due to the presence of minute colloidal droplets. The granular appearance is different in the two cell types. In the case of the serous cells they are fine, and when the gland is in the resting state, load the cytoplasm to such an extent that the nucleus is almost obscured. These droplets are believed to furnish the enzyme of the secretion, and are consequently termed *zymogen granules*. In the case of the mucous cells coarser *mucinogen granules* are seen. From these are derived the mucin which gives to the secretion of these cells its slimy character. When the glands enter upon secretory activity, the granules—whether zymogen or mucinogen—become less numerous as a result of their extrusion into the alveolus. After a prolonged period of secretion only a few remain in the region of the cell bordering the cavity of the alveolus, the rest having been discharged along with the water and other constituents of the juice. After a period of rest they accumulate again and gradually fill the cell.

THE CONTROL OF SALIVARY SECRETION

Two methods are at the body's disposal for the control of secretion. Glandular cells, in general, may be excited either through the mediation of nerves or chemically by the action of hormone (p. 670). When a quick response is required the nervous type of control is utilized. On the other hand, when rapidity of response is not a necessity, hormone control is employed. It will be seen later that some glands are controlled by both methods. Usually in such instances nerves

impulses initiate the secretion and hormones then maintain it over longer periods. It would appear that nervous energy is economized whenever it is possible for the secretion to be carried out efficiently by hormonal means. In the case of the salivary secretion a rapid response, in man and the carnivora at any rate, is obviously essential, since the food remains for such a short time in the mouth. Nervous mechanisms, therefore, are relied upon to bring about salivary secretion; there is no evidence of a specific hormonal mechanism. The salivary cells, however, are by no

lumar divisions of the autonomic nervous system (p. 938).

The submaxillary and sublingual glands receive their bulbar supply through the *chorda tympani* nerve. These fibers have the following course. Arising from the superior salivary center situated in the medulla in the region of the nucleus of the 7th nerve they leave the brain in the *nervus intermedius of Wrisberg* (p. 859). They pass without interruption through the genicular ganglion of the facial nerve and descend with the facial to the point where its *chorda tympani* branch is given off. They enter this nerve which upon approaching the cavity of the mouth joins the lingual nerve. In the floor of the mouth the secretory fibers leave the lingual again to make connections with the nerve cells of small ganglia. From these, postganglionic fibers arise which terminate by fine arborizations around the

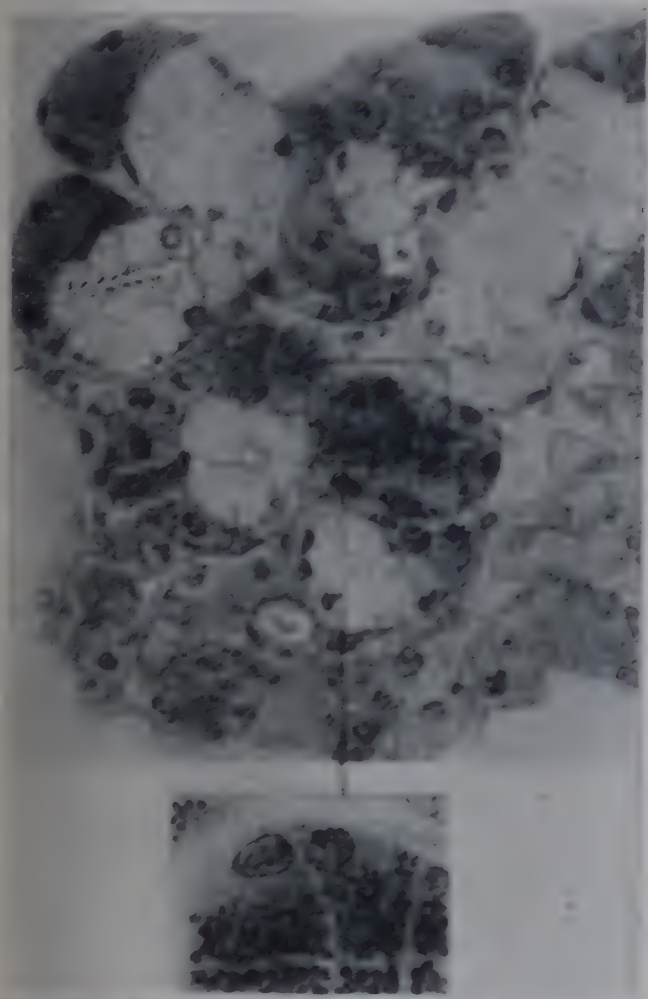


FIG. 181. Human submaxillary gland showing both mucous and serous groups of cells. Inserts are views with oil immersion, zymogen granules are clearly shown. (After Stormont, from Cowdry's *Special Cytology*.)

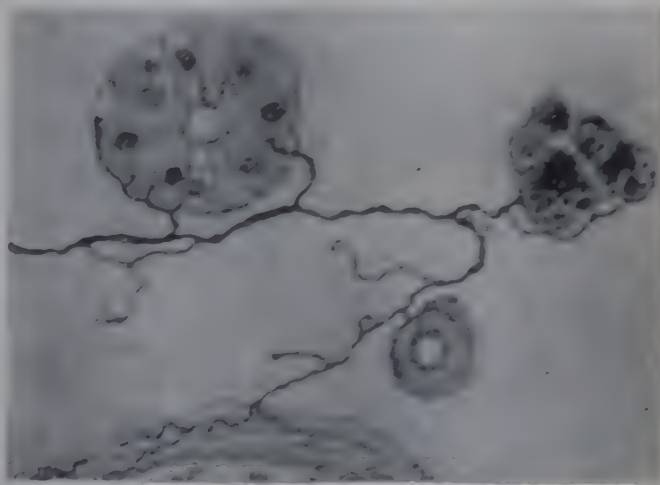


FIG. 182. Showing distribution of parasympathetic secretory nerves, to cells and blood vessels of submaxillary gland of rabbit. The serous cells are believed to be supplied by the parasympathetic, the mucous cells by the sympathetic. (From Stormont in Cowdry's *Special Cytology*.)

secretory (serous) cells (fig. 182). The ganglia furnishing fibers to the submaxillary gland are small and numerous, and are situated in the hilum of the gland. The sublingual gland contains no ganglion cells, it receives its postganglionic fibers from a small ganglion—the *submaxillary ganglion*—situated in the course of the *chorda* fibers just beyond their point of separation from the lingual and before they enter the gland (see diagram fig. 183).

The sympathetic supply (postganglionic fibers) is derived from the superior cervical ganglion. The fibers reach the gland via the plexuses of the external carotid artery and its branches. The preganglionic fibers arise from the upper one or two thoracic segments of the cord. Fine filaments end in the secretory (mucous) cells.

The *chorda tympani* also carries *dilator* fibers to the blood vessels of the gland; *vasoconstrictor* fibers are derived from the sympathetic.

The bulbar fibers to the *parotid* pursue the first part

Innervation of the salivary glands

The glands are supplied with secretory nerves from two sources—the bulbar and the thoracico-

means unsusceptible to chemical influences, for a number of substances, e.g., drugs and abnormal metabolic products, reaching them through the blood stream are capable of influencing their activity. Even though the salivary glands are under nervous control the immediate excitant of the gland cells is believed to be a chemical substance liberated at the nerve endings (see p. 946).

of their course in the glossopharyngeal, but they follow a devious path before finally terminating around the gland cells. They arise in the medulla from the *inferior salivary* center situated at the upper end of the nucleus of the glossopharyngeal nerve. At the jugular foramen they separate from the glossopharyngeal (petrous ganglion) in its *tympanic branch* (*Jacobson's N.*), and after passing into the trunk of the *small superficial petrosal nerve* are conveyed to the *otic ganglion*. There they communicate with ganglion cells from which postganglionic fibers arise. The

efferent salivary nerves depends upon which of the two types of nerve is chosen for the experiment. If the chorda tympani is stimulated, a profuse watery juice, poor in solids, results, the vessels of the gland dilate and the blood flow through it increases. The oxygen consumption of the gland is increased two- or three-fold. If a manometer be placed in the salivary duct and another in the carotid artery it will be found that when the chorda tympani is stimulated continuously the

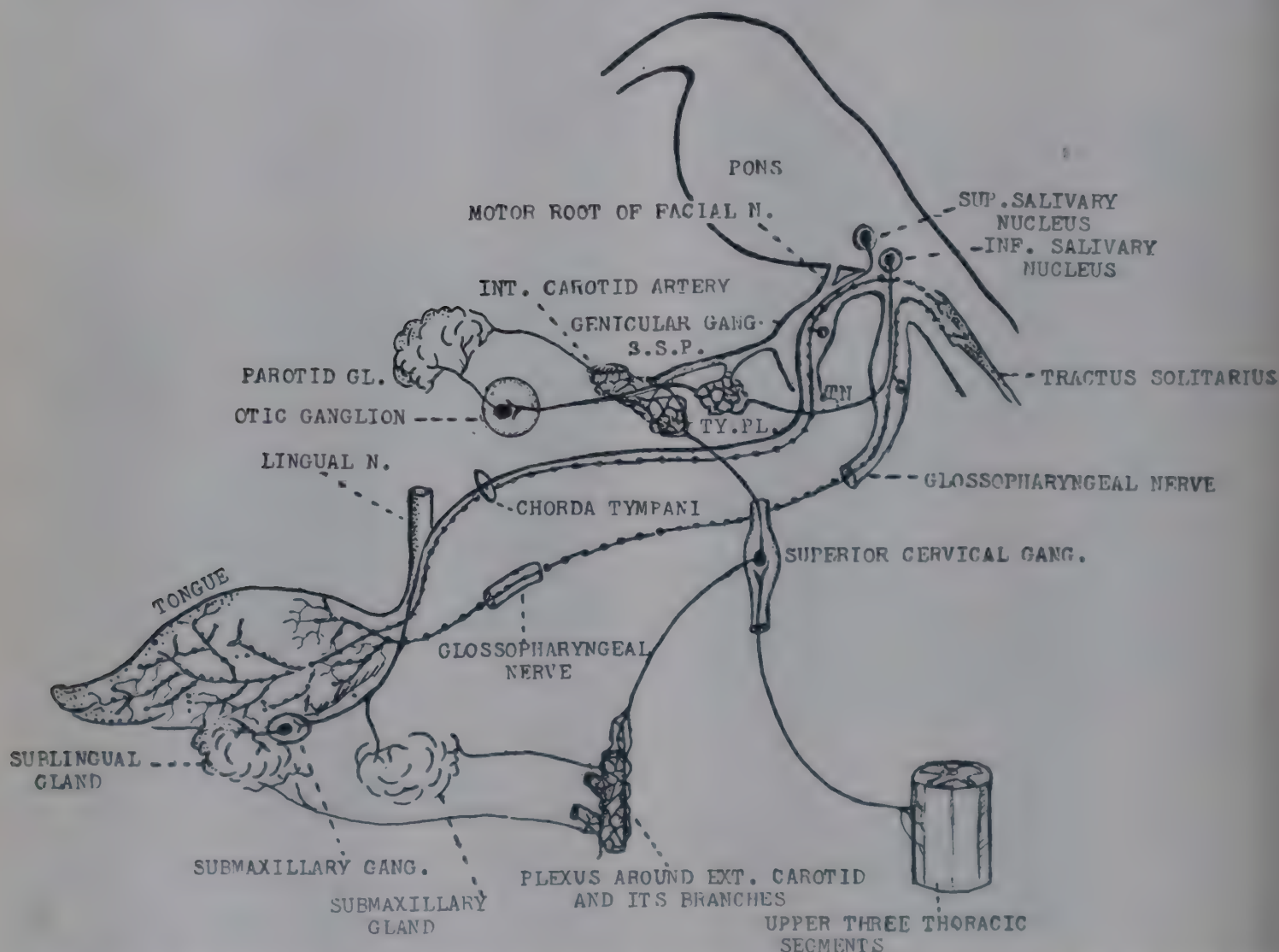


FIG. 183. (Diagrammatic.) Shows the innervation of the salivary glands and the course of the nerves of taste (beaded lines). S.S.P., small superficial petrosal nerve, TY.PL., tympanic plexus, TN., tympanic nerve.

latter are transmitted by the *auriculo-temporal* branch of the fifth nerve to the gland cells. The parotid also receives sympathetic fibers. The cell stations of the latter as in the case of the submaxillary and sublingual lie in the superior cervical ganglion. The dilator fibers to the blood vessels travel with the bulbar fibers. The vasoconstrictor fibers are furnished by the sympathetic, and follow the blood vessels into the gland.

EXPERIMENTAL STIMULATION OF THE SECRETORY NERVES

The nature of the secretory response which follows the electrical stimulation of one of the

secretory pressure ultimately rises above the blood pressure. This fact and the increased oxygen consumption of the gland during activity show that the production of saliva is a true secretory process and not simply due to filtration of fluid from the blood stream.

Stimulation of the auriculo-temporal nerve (parasympathetic fibers) to the parotid also causes an abundant watery secretion. Stimulation of the sympathetic fibers to the submaxillary or sublingual gland causes the secretion of small quantities of a thick mucinous saliva. No secretion

follows stimulation of the sympathetic supply to the parotid, though upon microscopical examination of the gland after such stimulation a reduction in the zymogen granules of the cells can be observed, which shows that sympathetic stimulation is not without effect. Stimulation of the cerebral cortex in the dog behind and below the cruciate sulcus causes the secretion of saliva.

THE REFLEX SECRETION OF SALIVA (ARTIFICIAL STIMULATION)

The salivary glands can be readily excited by the artificial stimulation of afferent nerves supplying structures in the mouth. The reflexes are brought about through the salivary centers. The *efferent* limbs of the reflex arcs—the secretory fibers of the chorda tympani and the tympanic branch of the glossopharyngeal respectively—have been considered above. The *afferent* pathways are along fibers contained in the trunks of the chorda tympani and glossopharyngeal nerves, in the lingual, buccinator and palatine branches of the fifth nerve and in the pharyngeal branch of the vagus. The fibers of the chorda tympani subserving the sensation of taste are distributed to the anterior two-thirds of the tongue. They arise from cells in the geniculate ganglion; the central processes of the ganglion cells enter the pons in the *nervus intermedius* of Wrisberg to make connections with cells in the tractus solitarius from which impulses are relayed to the superior salivary nucleus. The afferent fibers of the glossopharyngeal nerve concerned in the salivary reflex, carry sensations of taste from the posterior third of the tongue. They arise from cells in the petrous ganglion. The central processes of these cells enter the medulla to make connections through the tractus solitarius with the inferior salivary center (see also p. 860). The lingual fibers (cells of origin in Gasserian ganglion) furnish the general buccal mucosa with common sensation—touch, pain, etc. Secretion of saliva may be induced by stimulation of the central end of any one of these three groups of afferent fibers. It can also be brought about by stimulating sensory nerves in other situations. For example, experimental stimulation of the central end of the vagus, sciatic or indeed of practically any sensory nerve of the body may cause salivation. According to some, stimulation of afferent nerves of the gastric mucosa is particularly likely to initiate a reflex secretion into the mouth. In

disease, stimuli arising in the esophagus may cause profuse salivation (esophago-salivary reflex).

THE SECRETION OF SALIVA UNDER NATURAL CONDITIONS

In the normal life of the animal the secretion of saliva is brought about reflexly in two ways, either through (1) the stimulation of the nerves of the mouth by the presence therein of food or other substances, or (2) by the stimulation of some organ of special sense other than that of taste. The former type of reflex is termed *unconditioned* or *inherent*, the latter, *conditioned* or *acquired*. A reflex of one type does not, of course, exclude the other, and as a matter of fact both are called into play together under ordinary circumstances.

(1) *The unconditioned salivary reflex*

Materials placed in the mouth call forth after a short latent period (two or three seconds), a secretion of saliva which varies in *quantity* and *quality* with the physical and chemical nature of the substance introduced. The effects which sensations of taste produce upon the secretion of saliva are well known. Among edible substances, those, generally speaking, which are the most palatable or arouse the sensation of taste with the greatest intensity, are the most potent salivary stimulants. Substances that are entirely inedible will, if unpleasant to the taste—strong acids especially—cause profuse salivation. In these instances the secretion depends mainly upon the stimulation of the taste fibers and the stimulus is chemical in nature. But we have seen that stimulation, not only of the taste fibers (chorda tympani and glossopharyngeal) but of the fibers endowing the mucosa of the mouth with common sensibility (lingual nerve) as well will produce a salivary flow. So, materials such as dry sand, inedible powders, whether soluble or insoluble, or any other material which is capable of stimulating these endings in a purely physical way will evoke a secretion. The mere movements of the jaws and of the tongue over the mucosa of the mouth will have such an effect, though there is no material present in the mouth. A secretion occurs when any substance is chewed, whether or not it is edible or possesses taste. The chewing of india rubber (or gum) for instance, the manipulations of the dentist, the contact of his instruments with the oral mucosa or the grinding of a tooth are familiar and potent causes of salivation.

The remarkable *adaptability* or *purposeful character* of the salivary reflex has been remarked upon by Pavlov. The physical and chemical qualities of the juice, as well as its quantity are adapted to the physical or chemical characters possessed by the particular substance initiating the reflex. For instance, if clean pebbles be placed in a dog's mouth, they are expelled—merely allowed to drop out of their own weight. No secretion or very little occurs, since none is required; but if the stones are crushed and given as a powder, a profuse watery salivation follows to rid and cleanse the mouth of the useless material. The juice in this instance is poor in organic material and resembles that obtained upon electrical stimulation of the chorda tympani nerve or of the parasympathetic fibers to the parotid. Acid produces an abundant saliva which, according to Pavlov, is relatively rich in protein; this exerts a buffer action which reduces or annuls the injurious effect of the acid. The salivary response to the various foods is also adapted to their peculiar qualities. A chunk of meat, if given to a dog, is very quickly swallowed. Under the circumstances what is most required of saliva is a lubricant action. Accordingly, a highly viscous juice, rich in mucin is produced. If the meat be first dried and powdered, or if dry biscuit be fed to the animal the secretion is characteristic of parotid or chorda saliva—e.g., watery and abundant, but poor in mucin. Milk provokes a saliva rich in mucin, and foods, in general, produce a saliva rich in organic material—mucin and ferments—while inedible substances tend to call forth a more watery juice. These adaptations are much less pronounced in man.

The conditioned or acquired reflex

The secretion poured into the empty mouth when "the mouth waters" is the result of a conditioned reflex. The stimulus which initiates such a reflex is not applied to the nerves of the mouth but is received by one or other of the organs of special sense, particularly those of sight and smell. A conditioned reflex may also be elicited through the sense of hearing or through sensory impressions arising from stimuli applied to the skin. In brief, a conditioned reflex is one in which the cerebral centers play an essential part, and in which training and experience are the basis for the development of the reflex process. Conditioned reflexes are taken up in detail in Chapter LXX.

THE REACTION, QUANTITY AND COMPOSITION OF SALIVA

Human mixed saliva, according to the investigations of Starr is slightly acid in reaction. In 86 per cent of a large series of normal persons the pH was found to

vary between 6.35 and 6.85. The lowest pH found was 5.75 and the highest 7.05. Salivary reaction is dependent mainly upon the relative concentrations of free and combined CO_2 , that is, upon the ratio $\frac{[\text{H}_2\text{CO}_3]}{[\text{NaHCO}_3]}$.

So, in order that the true pH value be obtained the juice must be collected without loss of CO_2 . The older figures in the literature are too high (7.50 to 8.00) since this precaution was not taken. The hydrogen ion concentration of the saliva was found to vary directly with the CO_2 content of the blood. This means that when the CO_2 tension in the blood is high, more CO_2 finds its way into the salivary secretion to lower its pH, and vice versa. Forced breathing causes a lessened amount of CO_2 in the saliva, and consequently a rise in its pH. On the other hand, conditions associated with a retention of CO_2 in the blood cause increased excretion of the gas in the saliva, and an increase in its acidity. Ingestion of NaHCO_3 , while it reduces the acidity of the urine, increases that of the saliva, since a rise in the CO_2 tension in the blood results.

In man the amount of saliva secreted in 24 hours amounts to from 1000 cc. to 1500 cc. The cow secretes some 60 liters in the same time. Ordinary mixed saliva contains about 99.5 per cent of water and 0.5 per cent total solids. It has a specific gravity between 1.002 and 1.012. Its main constituents are as follows:

- I. *Salts* (approximately 0.2 per cent).
 - Sodium and potassium chloride.
 - Sodium bicarbonate.
 - Acid and alkaline sodium phosphates.
 - Calcium carbonate and calcium phosphate.
 - Potassium sulphocyanate.
- II. *Gases*.
 - Carbon dioxide, oxygen and nitrogen.
- III. *Organic substances*.
 - Ptyalin (salivary amylase) and maltase.
 - Serum albumin and globulin.
 - Urea, uric acid and creatine.
 - Mucin, mainly in the submaxillary and sublingual secretions.
 - Vitamin C.

The *bicarbonate* and to some extent the *phosphates* act as "buffers." The *chlorides* are necessary for the activation of the amylase. The *calcium salts* which are soluble in acid but insoluble in alkaline media tend to be thrown out of solution when the pH rises. The carbonate and phosphate of calcium may be deposited in the form of concretions (*salivary calculi*) within the ducts or, in combination with organic material, may be laid down upon the teeth as "tartar." A high salivary pH and a juice rich in mucin are believed to be conducive to tartar deposition and the development of calculi. The *potassium sulphocyanate* (KSCN) is an excretory product and is probably formed within the body from CN radicles derived from the metabolism of protein. Its production and excretion are thought to represent a detoxicating mechanism. It is said to be in

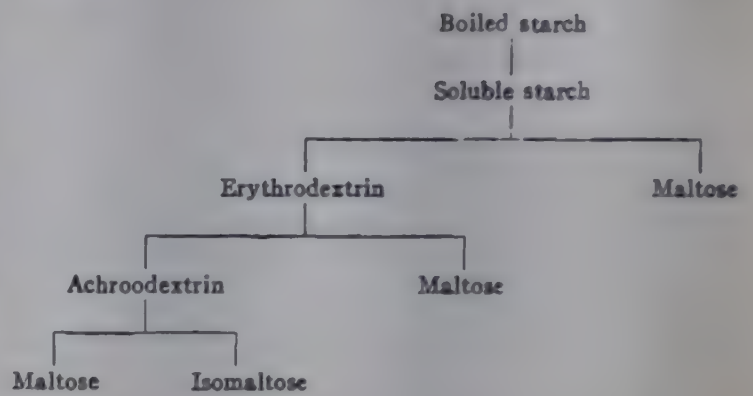
excess in the saliva of habitual smokers, and has been shown by Sullivan and Dawson to be noticeably reduced during the course of pellagra, but returns to normal value during convalescence from this disease.

FUNCTIONS OF SALIVA

(1) **DIGESTIVE.** The starch molecule is acted upon by the ptyalin and split into smaller molecules of the disaccharide maltose. The rapid passage of the food through the mouth precludes the possibility that it is acted upon here by the saliva to any important extent. Whether starchy food after its thorough impregnation with saliva undergoes any significant degree of digestion in the stomach has been debated. The salivary amylase requires for its activity an alkaline, neutral or but faintly acid medium. It was, therefore, thought that the highly acid gastric juice would prevent or soon terminate salivary digestion. It has been shown, however, that the latter part of the meal, which usually contains the carbohydrate, may remain in the fundus of the stomach protected for some time from the acidifying action of the gastric juice by a layer of food ingested previously. For this reason, it is likely that under favorable circumstances considerable digestion of starch is accomplished during this period. Bergeim found indeed, that 76 per cent of the starch of mashed potatoes was transformed into maltose in the human stomach.

If boiled starch be placed in a test tube with mixed human saliva and kept at body temperature, a slow conversion of the starch into maltose takes place. The chemical change occurs in a series of stages which may be distinguished by the manner in which the product of each reacts with iodine. Iodine gives a characteristic blue color with boiled starch. A short time after the saliva has commenced to act a physical change may be seen to have occurred in the starch. It loses its opalescent appearance and becomes *soluble*, though it still gives the blue color with iodine. After a short time the starch becomes partially broken down and converted into a dextrin which now gives a red color with iodine, and on this account is known as *erythrodextrin*. Small amounts of maltose may also be detected. Still later, no color reaction occurs upon the addition of iodine, a colorless dextrin—*achroodextrin*—has been formed. Finally the starch is entirely converted into maltose and isomaltose. In the final stage traces of glucose may also appear due to the presence in the saliva of a small quantity of mal-

tose. The following scheme illustrates these changes:



Ptyalin has no action upon cellulose and for this reason the starch must always be cooked in order that the cellulose envelope surrounding the starch grains may be broken. Boiling also causes hydration of the starch molecule itself, and renders it more easily disrupted by the amylase.

(2) **PREPARATION OF THE FOOD FOR SWALLOWING BY ALTERING ITS CONSISTENCY.** This is one of the most important functions of the saliva: the food is moistened, thus enabling it to be rolled into a plastic mass, and given a lubricant coating. Claude Bernard showed that a horse with parotid fistula had the utmost difficulty in swallowing dry hay or oats.

(3) **SOLVENT ACTION.** Taste is a chemical sense. All solid substances, in consequence, in order that they may stimulate the taste buds must be dissolved in the saliva.

(4) **CLEANSING ACTION.** The constant flow of saliva exerts a very necessary cleansing effect. The mouth and teeth are rinsed and kept comparatively free from food residues, shed epithelial cells, foreign particles, etc.; in this way the saliva inhibits the growth of bacteria by removing material which may serve as culture media. One has but to consider the foul condition of the mouth in certain fevers when the salivary secretion is suppressed, in order to realize how important its function is in this regard. Then, decomposing organic material swarming with bacteria (*sordes*) collects upon the teeth and lips, and must be removed by artificial means.

(5) **MOISTENING AND LUBRICATING ACTION.** The saliva by moistening and lubricating the soft parts of the mouth and lips keeps them pliable and resilient for the purposes of articulation. Frequent sips of water are almost essential for some public speakers, in whom as a result of evaporation from the mouth during speech, the supply of saliva is insufficient.

(6) **EXCRETORY.** Many substances both organic

and inorganic are excreted in the saliva. Drugs such as mercury, potassium iodide, lead, etc., when introduced into the body are excreted in part by the saliva. Severe inflammation of the oral mucosa (stomatitis) may be caused by the excretion of excessive amounts of mercury by this route. The blue line on the gum margins in lead poisoning is due to the metal having been excreted in the saliva, and deposited as the sulphide. The sulphur is provided by organic material contained in the tartar formed on the bases of the teeth. For this reason the discoloration of the gum does not occur where teeth are absent. In chronic nephritis the saliva contains a high percentage of urea; and sugar sometimes appears in severe diabetes; in parathyroid overdosage the calcium concentration of the saliva is elevated. Several types of microorganisms, some intensely virulent, e.g., the virus of hydrophobia and anterior poliomyelitis are excreted in the saliva. The latter disease has been reproduced in monkeys by injecting the saliva of an infected person.

In this connection it may be added that mumps, which is usually looked upon as a specific inflammation of the parotid gland, is more likely a general disease, since other organs, e.g. ovary, testicle, cerebral meninges, etc. unconnected in any way with the salivary glands are often seriously affected. The parotid inflammation is probably incidental and results from the passage of the infectious agent through the gland into the saliva.

(7) THE RÔLE PLAYED BY THE SALIVARY GLANDS IN THE REGULATION OF THE WATER BALANCE OF THE BODY. When the water content of the body is adequate the saliva is secreted continuously into the cavity of the mouth either by the main glands or by the innumerable small mucous glands that are scattered over the surface of the buccal mucosa. When, however, large quantities of fluid are lost from the body either through the sweat, bowels, kidneys, evaporation from the lungs or from the loss of blood, the salivary glands, in common with the other tissues, are subjected to the dehydrating effect; salivary secretion is suppressed. Drying of the oral mucous membranes, and the consequent stimulation of afferent nerves of the mouth and

pharynx arouses the sensation of thirst (p. 521). This sensation may be looked upon as an essential part of a protective mechanism against the depletion of body fluid. It serves to warn the individual that the body's water supplies require to be replenished.

The actions of drugs and chemicals upon salivary secretion

Serous secretion is stimulated by adrenaline, and ephedrine; acetylcholine, muscarine, pilocarpine, physostigmine (eserine), and histamine increase the mucus secretion. Atropine which antagonizes acetylcholine, and ergotamine which paralyzes sympathetic effects, inhibit secretion. Quinine paralyzes the effects of both nerves.

Disturbances of salivary secretion

Permanent suppression of the salivary secretion—*xerostomia* or *ptyalism* as it is termed—is an unusual condition; little is known regarding the mode of its production. Temporary suppression of salivary secretion is more common and occurs in emotional states and in fevers, or as already mentioned, when the water content of the tissues is lowered. Excessive salivation or *ptyalism* is not unusual and is often particularly troublesome in pregnancy, its cause in the later state is unknown; it is possibly of reflex origin, or due to some metabolic product acting in a drug-like manner upon the gland cells or the secretory nerves.

As a result of irritation of the gastric mucosa, in duodenal ulcer, or in lesions of the esophagus, such as carcinoma or spasm of the cardiac sphincter, salivation occurs as a reflex phenomenon, and may be pronounced (esophago-salivary reflex). The latter reflex is usually readily elicited in a normal person by the passage of a stomach tube or an esophageal sound. Since the glands respond to mechanical stimuli, painful or otherwise, the salivation associated with abnormal conditions in the mouth, e.g., a carious tooth, carcinoma of the tongue, etc. is not surprising.

When the reflex secretion is the result of stimuli arising in the stomach, esophagus or duodenum, and is excessive, the saliva may, without the individual's knowledge, pass down the esophagus and collect above the cardiac sphincter. The secretion occurs as a rule shortly after a meal and a short time later a large quantity of fluid may have accumulated, it may then be brought into the mouth in one or two gushes without any vomiting effort or even nausea. The condition is spoken of as *water-brash*.

CHAPTER XXXIX

GASTRIC DIGESTION

STRUCTURE OF THE GASTRIC GLANDS

The secretory cells of the stomach are arranged to form innumerable small individual tubular units, which constitute the gastric glands. These are scattered diffusely throughout the mucosa. Each opens by a single mouth into the bottom of a tiny pit—the *gastric foveola*. In some cases a single foveola receives the secretion of two or more glands. The gastric foveolae dot the mucosal surface in immense numbers; they are lined by columnar epithelium. The latter is of similar character in all parts of the stomach, and is continuous, on the one hand, with the general epithelial covering of the gastric mucosa, and, on the other, with the cells lining the *gland tubules*. In the latter situation the characters of the cells undergo a change, both morphological and functional, and acquire secretory powers of a special nature.

Each gland may appear as a single tubular structure which lies more or less perpendicular to the surface of the mucosa. More usually, its deeper portion is branched or shows an ill-marked bifurcation. The cellular elements of the glands of the fundus and of the greater part of the body of the stomach differ both in minute structure and in the nature of their secretions from those of the pyloric region as well as from those of the mucosa in the immediate neighborhood of the cardia.

(1) The glands of the fundus and body of the stomach

The gland tubule is divisible into a narrow and short superficial part—the *neck*, and a much thicker and longer portion—the *body*, which reaches nearly to the muscularis mucosae. Its blind extremity is club-shaped, indented or branched. The total number of the gastric glands has been estimated at 35,000,000. The cells which constitute the walls of the tubules are of three types: (a) *chief cells of the neck or mucous neck cells*, (b) *chief cells of the body or zymogenic cells*, and (c) *parietal or border cells*.

The *chief cells of the neck or mucous neck cells* together with the chief cells of the body form a continuous lining for the tubule, and upon a superficial examination resemble one another very closely. They are, however, quite different both in minute structure and function. Their morphological differences can be readily brought out by special staining methods. The chief cells of the neck contain granules of mucinogen but no zymogen

material. Their secretion is, in consequence, entirely mucuous in character. These cells are identical with those lining the entire length of the pyloric glands (see fig. 184).

The *chief cells of the body or zymogenic cells*, on the other hand, contain zymogen but no mucinogen

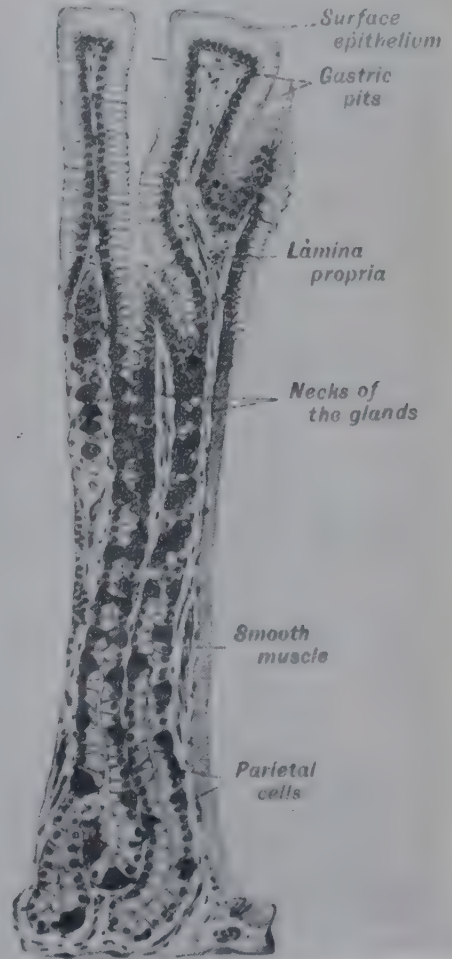


FIG. 184. Fundic glands of the human stomach. Zymogenic cells light; parietal cells dark. (From Maximow and Bloom, after Braus.)

granules. The former are composed of a material which is the precursor of *pepsin*. After grandular excitation the granules become markedly reduced in number; they accumulate again after a period of rest in the same way as has already been described for the zymogen granules of the salivary cells.

The *parietal or border cells* extend throughout the

entire length of the tubule, but are more numerous in the region of the neck. They do not, however, form a continuous layer, but are scattered here and there along the tubule and lie, not against the lumen, but between the chief cells and the basement membrane. They bulge the membrane outwards and in this way give an uneven, nodular or wavy contour to the gland. These cells can be distinguished from their neighbors not only by their location but by their staining reactions. They furnish the hydrochloric acid and the water of the gastric juice, and on this account, are also known as *oxyntic* or *acid secreting cells*. Though separated from the gland lumen by the chief cells they communicate with the former by means of delicate canaliculi which pass between the chief cells. These canaliculi are extensions of a canal system consisting of an exquisitely fine meshwork *within* the body of the parietal cell. Coarse transparent granules are seen in the protoplasm of the parietal cells during rest; depletion of this granular material occurs during activity.

(2) The pyloric, esophageal and cardiac glands

The pyloric glands are shorter but run a more tortuous course. Parietal cells are absent, and the tubules are lined entirely by cells of the same type as the mucous neck cells of the fundic glands. The pyloric glands, in consequence, are capable of forming mucus but not of supplying pepsin or hydrochloric acid to the gastric juice. Their secretion is alkaline in reaction. The glands in the immediate neighborhood of the cardiac orifice—cardiac glands—are also of the purely mucous type and secrete an alkaline juice. Glands almost identical in character are present in the esophagus—at the level of the cricoid cartilage and at its lower end just above the cardia.

THE GASTRIC JUICE; COMPOSITION; ORIGINS AND DIGESTIVE ACTIONS OF ITS CONSTITUENTS

(SEE ALSO INTRINSIC FACTOR, P. 64)

COMPOSITION

The gastric juice is a mixture of the secretory products—pepsin, mucin, and a watery solution of acid—of the three types of cells composing the gastric glands; it also contains a variable quantity of mucous secreted by the surface epithelium.

The main digestive action of the gastric juice is exerted upon protein, which is split into smaller groups of amino acids by *pepsin* and *hydrochloric acid*. It also contains *rennin* which curdles milk and a very weak lipolytic ferment—*gastric lipase*. The composition of fasting human gastric juice as obtained through a fistula is given in the following table (modified from Carlson).

Acidity	Free HCl, 0.40 to 0.50 per cent
	Total acidity, 0.45 to 0.60 per cent
	pH, 0.9 to 1.5

Solids	Organic, including mucin and the various ferments, 0.42 to 0.46 per cent
	Inorganic, 0.13 to 0.14 per cent
Specific gravity, 1.006 to 1.009	
Total nitrogen, 0.051 to 0.075 per cent	

HYDROCHLORIC ACID IN THE GASTRIC JUICE

Prout in the early part of the last century (1824) first demonstrated the presence of hydrochloric acid in gastric juice. The only other instances of a strong acid being formed by living processes is the production of sulphuric acid, probably for defence purposes, by certain molluscs, and the presence of a fluid with a pH as low as 1.0 in the vacuoles of some unicellular organisms. It has been already mentioned that the parietal cells of the fundic glands are responsible for the production of the acid and water of the gastric juice.

The secretion of the parietal cells cannot be collected separately from the other constituents of the gastric juice and, therefore, cannot be subjected to direct analysis. Its composition can be arrived at only by inference. Hollander analyzed canine gastric juice collected from a stomach pouch and has inferred the composition of pure parietal secretion from the fact that, with increasing acidity, the other constituents decline. The acidity when plotted against the neutral chloride gives a straight line expressing an inverse relationship between them. When extrapolated this line comes to a point representing a zero value for neutral chloride and an acidity of 170 m. eq. per liter. From this it is concluded that pure parietal secretion is an isotonic fluid containing approximately 170 m. eq. HCl per liter and free from neutral chloride. Pavlov had come to the conclusion that the acidity of the gastric juice as it left the glands remained constant (regardless of the rate or volume of secretion) at a concentration of about 0.5 per cent. Pavlov's belief in the constancy of the acid concentration as secreted by the glands is supported in the main by Hollander's experimental results and this view is now widely held.

Gray has calculated the energy required for acid production and arrives at a figure of 1.5 calories for a liter of parietal fluid. Accepting the carbonic anhydrase theory of acid formation, he concludes that this amount of energy is probably furnished by the oxidation of about 5 grams of glucose.

The contents of the human stomach after the usual test meal have a total acidity of from 5 to

40 clinical units (p. 439) or from 0.02 to 0.15 per cent of total acid. The gastric juice secreted into the empty stomach after the more powerful stimulus of histamine injection or in response to psychic stimulation has a total acidity of from 80 to 140 clinical units and a pH of from 1.0 to 1.2. At the height of digestion of a mixed meal containing meat, the acidity of the gastric contents may approach that of juice secreted under the influence of histamine. The low acidity of the human gastric contents after a test meal is due to the latter's relatively mild stimulating effect upon the glands as well as to the dilution and neutralization of the juice by saliva, mucus and other constituents of the meal itself. The analyses of histamine juice, as noted above, and of pure juice collected from a fistula indicate, however, that human gastric juice as it is secreted by the glands has probably an acidity equal to that of canine juice.

There is a relationship (in dogs and human subjects) between the acid concentration in the gastric juice and the erythrocyte count (Apperly and Cary). In severe anemia due to hemorrhage free acid disappears from the gastric juice; as blood regeneration occurs it reappears, its concentration increasing to a maximum when the red cell count reaches the normal value. If the erythrocyte count rises above the normal level (e.g., in polycythemia) the acid concentration steadily falls again to low values.

The origin of the hydrochloric acid

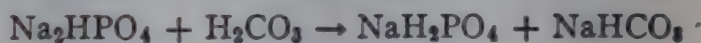
Claude Bernard was one of the first to investigate the question of the origin of the acid. He injected potassium ferrocyanide and lactate of iron into an animal's veins. These substances give the Prussian blue reaction in the presence of free mineral acid. The mucosa of the stomach was turned blue after the injection, but no discoloration was observed in the gland cells or in the lumina of the glands. He concluded, therefore, that the glands secreted some unknown product, which, upon reaching the surface of the mucosa, gave rise to the acid.

Similar experiments were carried out by Fitzgerald, and later, vital dyes which changed color at definite pH values were employed by Harvey and Bensley. The results of these two groups of investigators were not in agreement, the former claiming that the acid was formed within the fine intracellular canaliculi, the latter that it was formed within the lumen of the tubule. Harvey and Bensley suggested that NH_4Cl was secreted into the tubules and through selective re-absorp-

tion of ammonia, HCl was formed. Subsequently, however, Ivy by mean of a Pavlov pouch and the use of vital dye indicators demonstrated that during secretion the cells have a pH ranging somewhere between 6.8 and 3.0. A more precise value was not determined, but the result indicates that the site of acid formation is definitely intracellular.

The ultimate source of the acid is undoubtedly the sodium chloride of the blood. Kahn showed many years ago that, if an animal be fed for some weeks upon meat, deprived of its chlorides by prolonged boiling in distilled water, acid-free gastric juice was secreted. Also the continued loss of gastric juice from the body results in a marked fall in blood chloride. If bromide is fed to an animal which has been deprived of salt for some time hydrobromic acid appears in the gastric juice.

Several theories of the chemical processes concerned in the formation of hydrochloric acid from the blood chloride have been advanced. Many believed reactions represented by the following equations were responsible



Collip by microchemical methods obtained important evidence in support of this conception. He found that the parietal cells are exceptionally rich in phosphates, but during rest chlorides are absent. When the glands became active however a remarkable increase in the cell chlorides occurred. Nevertheless, it is difficult to detect any difference between the concentrations of chloride in the arterial and venous bloods of the gastric mucosa.

The relationship between the CO_2 content of the blood and the secretion of acid in the gastric juice has been demonstrated by several workers. Hyperventilation (blowing off CO_2) reduces, and breathing CO_2 rich mixture increases, the acid secretion. Apperly and Crabtree found that the gastric acidity in man varied directly with the bicarbonate content of the plasma. Browne and Vineberg have demonstrated that the gastric secretion induced by vagal stimulation in dogs is inhibited when the CO_2 content of the plasma falls below 30 volumes per cent as a result of hyperventilation but is restored again when the CO_2 percentage of the inspired air is raised.

Davenport has reported a high concentration of carbonic anhydrase in the parietal cells of the gastric mucosa, and suggests that acid secretion is

proportional to the rate of formation of H_2CO_3 from CO_2 and H_2O . It is significant that thiocyanate and sulphanilamide inhibit the action of carbonic anhydrase as well as the secretion of acid by the gastric mucosa of dogs. These observations have led to the formulation of the *carbonic anhydrase theory* of acid production by the gastric mucosa. According to this theory, as advanced by Davenport, the acid is formed by a reversed chloride shift. It will be recalled (p. 106) that the blood in passing through tissues, such as muscle, receives CO_2 which diffuses into the red cells and is there hydrated to H_2CO_3 by the action of carbonic anhydrase. The carbonic acid ionizes, the HCO_3 ion diffusing into the surrounding plasma and the Cl ion from the plasma into the cells. Electrical equilibrium is thus maintained. In the gastric mucosa H_2CO_3 is formed from CO_2 by the action of carbonic anhydrase, the bicarbonate ion (HCO_3) then diffuses into the plasma and from the plasma into the red cells leaving the H ion in the gastric mucosa. Chloride ions leave the red cells (reversed chloride shift) and pass then from the plasma into the parietal cells; here they are united with H ions to form HCl .

The relation of gastric secretion to the acid-base-balance

A reduction in the excretion of acid by the kidney—the so-called *alkaline tide of the urine*—occurs after a meal. This was attributed to the loss of HCl in the gastric juice. Higgins, and later, Dodds and Bennett found that a rise of from 2 to 5 mm. in the CO_2 tension of the alveolar air occurred half an hour or so after meals; a corresponding fall below the normal level was reported to follow about one and a half hours later. These changes have been looked upon as compensatory reactions brought about by the loss of acid in the gastric juice, and of alkali in the pancreatic juice, respectively, which served to maintain the normal acid-base balance of the body fluids. Though the reduced excretion of acid by the kidney and the rise in the CO_2 tension of the alveolar air and plasma do actually occur during normal gastric digestion, recent work has seriously questioned the generally accepted explanation that the phenomena are due to the secretion of HCl (see p. 395).

When, on the other hand, abnormally large quantities of gastric juice are lost from the body, as in pyloric obstruction with persistent vomiting, or in intestinal obstruction, a profound effect upon the acid-base balance is produced. A fall in blood chloride leading to a state of compensated or uncompensated alkalosis results; tetany may occur. Dragstedt and Ellis have also shown that, in animals, drainage of the gastric juice to the exterior through a fistula results in a reduction of 50 per cent in the blood chloride, alkalosis,

marked dehydration and a rise in the nonprotein nitrogen of the blood. Severe depression occurred ending in death.

THE ORIGINS AND ACTIONS OF THE GASTRIC ENZYMES

PEPSIN is derived from the chief cells of the fundic glands. The zymogen granules in the cytoplasm of these cells are believed to represent the mother substance of the active ferment. Pepsin is active only in acid media; the optimum pH value for its action is about 1.5 (Sorensen). The optimum pH varies, however, in accordance with the particular protein which is being digested. Thus, the optimum pH for the digestion of casein is 1.8, for the digestion of gelatin 2.2. At a pH of 5.0 the action of pepsin is almost abolished. The digestive action of pepsin is confined to protein which it splits into proteoses and peptones. Northrop has obtained pepsin in crystalline form; it is protein in nature.

The first stage in peptic digestion is the action of the acid upon protein to form *acid metaprotein*. The latter is insoluble in water and neutral solutions but soluble in the acid secretion of the stomach. The acid metaprotein is then acted upon by pepsin. The protein molecule is constructed of many amino-acids (p. 538), the greater proportion of which, it is generally believed, are linked together by their amino (NH_2) and carboxyl (COOH) groups. This is spoken of as the *peptide linkage*. The function of the different proteolytic enzymes of the digestive juices (gastric, pancreatic and intestinal) is to break the protein molecule into smaller and smaller fragments containing successively fewer numbers of amino-acids. A molecule of water is taken up (hydrolysis) as the first step in the process and cleavage occurs at the $\text{CO} - \text{NH}$ junction.¹ In the final stage of protein disintegration the molecule is completely disrupted and its individual "building stones"—the amino-acids—separated from one another. This ultimate stage must be reached before protein material can be made use of by the body. Gastric digestion of protein does not go beyond the peptone stage. The action of pepsin (in vitro) is reversible. Wasteney and Borsook have demonstrated the synthesis of protein by pepsin from a concentrated

¹ Though this type of cleavage is unquestionably effected by the pancreatic and intestinal proteolytic enzymes, some have doubted that pepsin is capable of breaking the peptide linkage and have suggested that it attacks some other type of linkage in the protein molecule (see diketopiperazine linkage, p. 540). The evidence, however, is strongly in favor of the view that the peptide linkages are broken by peptic action.

peptic digest of albumin. The optimum hydrogen ion concentration for the synthetic action is at pH 4.0.

GASTRIC RENNIN (OR RENNIN). This, the milk-curdling ferment, is generally believed to be a product also of the chief cells of the fundic glands. Its concentration is low in the gastric juice of the adult. According to some observers, it is absent from adult human gastric juice, the milk-curdling power of the juice being due to pepsin. Rennin is especially abundant in the gastric mucosa of young animals while pepsin is present in minimal amounts. The optimum pH for the action of rennin is between 6 and 6.5 and it is quite inactive at the pH of the gastric contents of the normal adult. In the infant, however, the pH of the gastric contents (5 to 6.5) is around the optimum for the action of this enzyme.

The clotting of milk by rennin shows a certain resemblance in several of its chemical and physical features to the clotting of blood (p. 88). In each instance a soluble protein is rendered insoluble as the result of the activity of a ferment, and in order that this shall occur it is necessary that calcium salts be present in ionized form. In both processes a clear incoagulable fluid, whey in the case of milk, serum in the case of blood, can be expressed or separates spontaneously when the coagulum is allowed to stand. Oxalates and citrates by precipitating the calcium prevent the clotting of either of these fluids. Gastric rennin when added to milk kept at body temperature causes a change in the soluble *casein* (caseinogen) splitting it into a *proteose-like* substance (*whey protein*) which remains in solution, and *paracasein*. The latter is soluble itself but upon combination with calcium forms an insoluble compound, *calcium paracasein* which is thrown down to form the clot or curd. The protein (paracasein) of the curd subsequently undergoes peptic digestion in the usual manner. The softer and more finely flocculent the character of the curd that is formed, the more readily is it attacked by the proteolytic ferments. According to Pavlov the admixture of mucus with the milk renders the resulting curd softer in consistency.

Gastric lipase is a weak fat-splitting enzyme. It differs in an essential manner from the lipases of the pancreatic and intestinal juices in that it acts in an acid medium, and is reduced in activity and finally destroyed by alkali. Its pH optimum ranges between 4 and 5. At a pH of 2.5 its action ceases. It is assumed that gastric lipase is also secreted by the chief cells of the fundic glands, though proof of this is lacking.

Owing to its very weak action gastric lipase is of little practical importance, in adults at any

rate. It is soon rendered inactive as the acidity of the gastric contents rises during digestion, and any action which it may have, is exerted only upon fats in a state of very fine emulsion, e.g., milk, yolk of egg, etc. On this account it may possibly be of greater importance in infants in whose stomachs it is found at, or shortly after birth, and whose gastric contents have a pH more favorable for its action. The whey of mother's milk is said to enhance the action of gastric lipase in infants. Nevertheless, it is questionable whether this enzyme even in infants possesses any real digestive value.

According to some observers digestion of fat in the stomach may be accomplished by pancreatic lipase that has regurgitated through the pylorus. But since pancreatic lipase acts best in a decidedly alkaline medium its optimum pH being 8, and very weakly in an acid medium, its action must be slight so long as the gastric juice possesses its normal acidity. If, however, this is depressed or absent the gastric digestion of fat may be effected to a considerable extent by this means. It is to be remembered in this connection that a meal of fat depresses gastric acidity. Fat also increases duodenal regurgitation which by aiding neutralization may bring about the reaction suitable for the activity of pancreatic lipase.

Gastric mucin

Mucin is a glycoprotein (p. 539). It is secreted by the cells of the pyloric and cardiac glands and by the mucous neck cells of the fundic glands. It is therefore a constituent of pure gastric juice (dissolved mucin). It is also a constituent of the mucous secretion of the ordinary epithelial cells (goblet cells) of the gastric mucosa (surface epithelium mucus). Ivy found that the juice collected from pouches fashioned from the pyloric part of the stomach of dogs was mucoid, viscous, tenacious and transparent with a pH of 7.0 to 7.5.

Gastric mucin has a high acid combining power. It coats the interior of the stomach, and by reducing the free hydrochloric acid serves to protect the mucosa from the action of the gastric juice. Quite apart from its power to lower the acidity of the gastric juice Babkin and Komarov find that mucin inhibits peptic activity. This anti-peptic action of mucin is due to its constituent, mucoitin-sulphuric acid. The protective properties of gastric mucin have been put to practical use by Fogelson and by Ivy and Kim, in the treatment of gastric and duodenal ulcer. The mucin is prepared from hog's stomach. One gram of such a preparation combines with

15 cc. of a 0.5 per cent hydrochloric acid and Fogelson found that about 60 grams was more than sufficient to neutralize the acid secreted in response to the injection of 1 mg. of histamine. Also when $\frac{1}{2}$ ounce of mucin together with 1 pound of meat was given to a dog, free acid did not appear in the stomach until the lapse of from 5 to 7 hours.

THE CHYME

The changes in the food brought about by the various chemical and physical processes that have been described as constituting gastric digestion may be briefly summarized. Much of the *protein* of the food is reduced to simpler materials which are soluble in the fluids of the stomach. The *fats* undergo some degree of emulsification. Other materials, such as the *sugars* taken preformed with the food or those derived from the partial digestion of the *starches*, pass readily into solution. The remainder of the *starch* is in part rendered soluble (soluble starch and dextrins) by salivary action and in part reduced to a fine state of mechanical division. The gastric movements (p. 484) cause these various elements, which differ widely in their chemical and physical natures, to become thoroughly mixed with one another and with the gastric juice until finally the food assumes a semi-fluid, more or less homogeneous, creamy or gruel-like consistency. This material, now known as the *chyme* (Gk. *chumos*—juice) is definitely acid in reaction; it passes through the pyloric opening, not all at once but from time to time as it is formed. The food having reached this stage is suitably prepared for further digestion by the intestinal juices.

THE RELATIVE IMPORTANCE OF CHEMICAL AND MECHANICAL FACTORS IN GASTRIC DIGESTION

Borelli and the mechanical school of physiologists of the seventeenth century saw digestion simply as a process in which crushing, grinding and mixing of the food, and the expression of its nutritive juices were the prime features. Chemical processes were scarcely considered. The second stomach or gizzard of the bird in which resistant objects, even glass beads, are crushed was pointed to in support of these mechanical conceptions of gastric digestion. Not until the experiments of Réaumur (1683–1757) and Spallanzani (1729–1799) was the chemical character of gastric digestion appreciated. They showed

by a crucial experiment—the digestion of meat by gastric juice in a test-tube—that gastric digestion was a chemical process, and not simply a mechanical disintegration of the food. Ever since, more stress, perhaps, has been laid upon the chemical than upon the mechanical side of digestion. It is probable, however, that the latter is in reality of just as great or even of greater importance than the chemical factor. Subjects in whom the gastric juice is entirely absent usually suffer no apparent difficulty in the digestion of food and there may be no gastric symptoms whatsoever. The larger part of the stomach may be removed and, provided that the consistency of the food is made suitable, little digestive inconvenience results. After complete removal of the human stomach, protein and fat digestion have been found to be perfectly normal, but there may be depression of intestinal motility as a result of the unavoidable severance of the vagus nerves. Purely mechanical factors, on the contrary, very frequently give rise to digestive disturbances, and it is probably true that the *immediate* factors responsible for the production of the various symptoms of gastric disease are always mechanical in nature. Disturbances of gastric motility, for example, may cause discomfort, pain and other dyspeptic symptoms. The stomach contents may be retarded in their passage into the duodenum as a result of spasm of the pylorus or of an organic blockage. On the other hand, a too rapid evacuation of the stomach may, by permitting food to enter the duodenum in an improperly prepared state, induce ill effects. The chemical processes of gastric digestion, therefore, important as they are, must not be allowed to overshadow in our minds the mechanical factors. A prime function of the stomach is to break up the food, to add fluid to it and reduce the entire mass to a semi-fluid consistency, in which state it can be more readily acted upon by the digestive enzymes of the intestine. The movements of the stomach will be discussed in Chapter XLIII.

THE ANTISEPTIC ACTION OF GASTRIC JUICE. By virtue of its high acidity normal gastric juice has an important bactericidal action. Streptococci, staphylococci and *B. coli* are destroyed, the contents of the duodenum in health being virtually sterile. In permanent or temporary achlorhydria, on the contrary, the duodenum is very quickly invaded with microorganisms from the colon. Following perforation of a gastric or duodenal ulcer, for example, the gastric secretions are suppressed as a result of the shock occasioned by the accident, and peritonitis supervenes.

after sufficient time has elapsed for the duodenal fluids to become infected in this way. The importance of early operation is self evident.

The Effects of Gastrectomy upon Certain Non-digestive Functions. Since the stomach plays an important part in erythropoiesis (p. 64), it might be expected that anemia of the pernicious type would follow its removal but, as a matter of fact, pernicious anemia is rarely seen after total gastrectomy either in man or in animals. The microcytic hypochromic type, on the other hand, is not uncommonly a result and is most probably due to defective absorption of iron caused by the lack of hydrochloric acid (p. 60). It responds to iron administration. Ivy and his associates have reported rarefaction of the bones in puppies leading to gross deformities of the limbs following gastrectomy. Removal of the stomach in growing monkeys caused

arrested growth and a condition of the bones resembling osteitis fibrosa cystica (p. 708), together with hypocalcemia and enlargement of the parathyroid glands. The condition is the result apparently of impaired calcium absorption due in turn to the absence of hydrochloric acid (p. 711); of it can be prevented to a large extent or partially corrected by adding soluble calcium salts to the diet. As well as the one just mentioned, Ivy lists three other causes of the osteoporosis; (a) the absence of the reservoir function of the stomach, imperfectly digested food being passed rapidly through the upper part of the intestine from where the greater part of the calcium is normally absorbed; (b) the postprandial acidosis resulting from the secretion of alkaline intestinal juices in the absence of the acid gastric secretion and (c) encroachment of the red marrow (due to the anemia) upon the osseous tissue.

CHAPTER XL

GASTRIC DIGESTION (*Continued*)

THE SECRETION OF GASTRIC JUICE

THE INNERVATION OF THE GASTRIC GLANDS

Stimulation of the vagus nerve causes the secretion of juice high in peptic power and strongly acid. According to Alley and Babkin the glands of the lesser curvature respond more readily to vagal stimulation than do those of the greater curvature, and secrete a stronger juice. This fact may be of significance in the development of gastric ulcer (p. 443). Baxter has shown that stimulation of the sympathetic causes the secretion, mainly from the pyloric glands, of an alkaline mucoid juice which is very low in peptic power; this secretion is unaffected by atropine but is annulled by ergotamine (which paralyzes motor and secretory sympathetic fibers). Vineberg's results indicate that the vagus controls the secretion of mucus by the mucous neck cells and the surface epithelium of the gastric mucosa. The influence exerted by the sympathetic upon the peptic and oxyntic cells is not definitely known. According to some observers its effect upon these elements is inhibitory.

THE QUESTION OF THE CONTINUOUS OR INTER-DIGESTIVE SECRETION OF GASTRIC JUICE

Pavlov found that the secretion of gastric juice in dogs was intermittent; beyond the secretion of some alkaline mucus the gastric glands in the absence of food or psychic influences (see below) remained at rest. This conclusion has been confirmed by the recent experiments of Babkin. But in man, juice is secreted continuously in fairly large amounts; but this fact does not necessarily indicate a fundamental difference between the activities of the glands of the human and canine stomachs. The shorter intervals between meals, and psychic influences which are impossible to eliminate in the case of the human subject, are probably responsible for the continuous and apparently spontaneous secretion. The secretion is increased during sleep.

THE PHASES OF GASTRIC SECRETION

It has been known for many years that it is not a necessary condition for the excitation of the gastric glands that food shall enter the stomach.

The mere presence of food in the mouth calls forth an abundant secretion of gastric juice. The flow of juice that occurs in this instance is due to a nervous reflex and is termed the *psychic or cephalic phase of gastric secretion*. It is also well known that the glands are stimulated by the presence of food in the stomach, even after all nerves connecting the organ with the central nervous system have been severed. This secretion of gastric juice which results from influences arising within the stomach itself is referred to as the *gastric phase*. Secretion of juice also results from influences arising from the intestine after the food has passed through the pylorus. This is the *intestinal phase of gastric secretion*.

THE PSYCHIC OR CEPHALIC PHASE

The psychic secretion of gastric juice was originally demonstrated by Pavlov, in dogs. To study in detail this phase of gastric secretion and other problems in gastric physiology he devised the following operation. A longitudinal incision was made in the body of the stomach in the region of the greater curvature (fig. 185AB). This included both anterior and posterior walls of the organ, and starting near the pyloric region ended about the middle of the fundus. The concave flap formed in this way, and which remained attached to the fundic region by its base, was then turned down and its cut edges, as well as those of the main stomach, sutured together. Thus was fashioned a small tube lined by normal gastric mucosa with an open free end (fig. 185S). Complete isolation of the cavity of the tubular pouch from the main cavity of the stomach was accomplished by reflecting a flap of mucosa from the gastric walls at the junction of the pouch with the fundus and fixing it in position to form a partition between the two cavities. The free, open end of the pouch, or *miniature stomach*, as it is usually called, was then sutured into the abdominal wound. Through the fistula established in this way pure gastric juice uncontaminated by food could be collected while digestion was proceeding normally in the remainder of the stomach. The main stomach was also fastened to the abdominal wall and a fistulous communication established between it and the exterior. The advantage of

this operation over previous ones contrived for a similar purpose (e.g., the Heidenhain pouch) is that, on account of the longitudinal direction of the incision, a minimum amount of damage is inflicted upon the nerve supply of the pouch.¹ Furthermore, a comparatively large pouch—about one-tenth the size of the whole stomach—is procured by this means. The miniature stomach is assumed to portray faithfully the behavior of the main stomach under various experimental conditions. This assumption has been justified by control

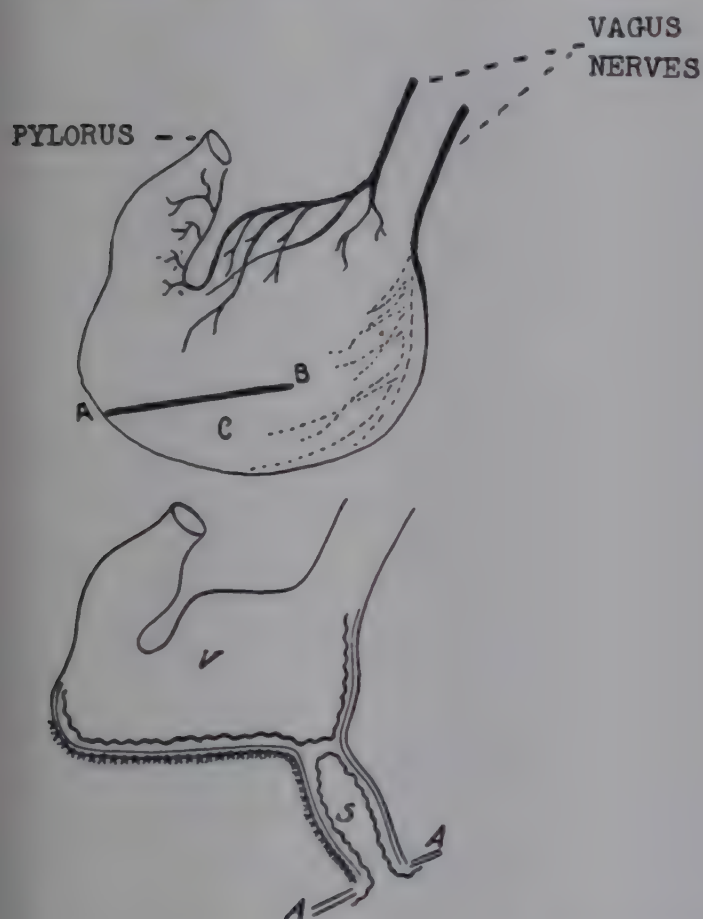


FIG. 185. The Pavlov pouch. Upper drawing shows line of incision to form a flap. C, cardiac part of stomach. Lower drawing shows the completed operation. S, pouch; the mucous membrane has been reflected to form a partition between the main cavity of the stomach and the miniature stomach. A, A, abdominal wall (after Pavlov).

experiments in which the secretion of the miniature and of the main stomach were compared.

Sham feeding

In the study of the psychic phase of gastric secretion it is, of course, essential that no food shall be allowed to enter the stomach. In order to secure this the esophagus was divided in its upper third; the lower end of the upper section was then brought out through the skin wound and fixed in position by sutures (fig. 186). A miniature stomach and a gastric fistula leading into the main

¹ This claim according to Jemerin and Hollander is unwarranted.

portion of the stomach were also produced, in the manner already described, for the purpose of observing the secretory responses, as well as for feeding the animal when necessary. An animal prepared in this way could eat and enjoy its meals but the food after being swallowed simply issued from the esophageal opening in the neck. When "*sham or fictitious feeding*," as this procedure is called, is performed a profuse secretion of gastric juice follows after a brief latent period. In some experiments in which sham feeding was maintained for 5 or 6 hours, as much as 700 cc. of pure gastric juice were secreted into the stomach. A proportionately smaller amount was secreted into the artificial pouch. Even after a single 5-minute

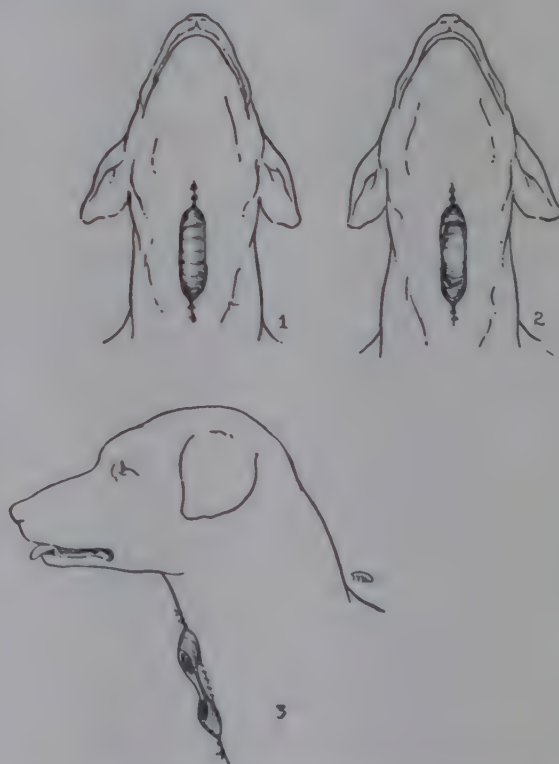


FIG. 186. A two-stage operation for making an esophageal fistula. 1. First stage, showing esophagus exteriorized. 2. Second stage, performed four or five days later, showing excision of elliptical segment of anterior esophageal wall. 3. Completed operation, lateral view. (After Dragstedt and associates.)

period of fictitious feeding the secretion persists for from one to three hours, and produces 200 or 300 cc. of juice. The secretion is rich in pepsin. Division of the vagi completely abolishes the response. It is, therefore, undoubtedly due to a reflex mediated through these nerves. The quantity of juice varies with different foods, but the only quality of the food which appears to influence the psychic secretion is its palatability; the chemical or physical properties of the food are unimportant in this regard. Meat for instance for which the animal has a keen relish produces a juice of the greatest abundance and richest in ferment. Bread or other materials not particu-

larly appetizing cause less secretion, and the juice has less digestive power. A more pronounced reaction occurs if the animal is hungry. In marked contrast to the activity of the salivary glands, no secretion can be evoked by placing inedible substances in the mouth, or those which are injurious or nauseous, such as acid, pepper, asoefetida, etc. Indeed these may cause inhibition of a secretion that is already in progress. All these facts point to the involvement of the higher nervous centers in the reflex mechanism. The pleasure of eating, the agreeable stimulation of the organs of taste and the gratification of appetite are essential conditions.

It is not even necessary that the food should enter the mouth in order to elicit the gastric response. Provided the food is sufficiently appetizing simply sight or smell of it will cause secretion. In other words a *conditioned reflex* can become established for gastric as well as for salivary secretion (p. 420).

The importance of the psychic secretion may be judged from the fact that in its absence gastric digestion is seriously hampered. When, for example, a piece of meat or bread is placed in the stomach through a fistula while an animal is sleeping or, by the diversion of its attention, is unaware of the introduction of the food, much less is digested in a given time than when the animal has been shown the food before introducing it into the stomach or has been given it by "sham feeding."

Babkin has shown that a time element may be prominent in the conditioned response; he found that animals which were accustomed to being fed at a certain hour each day secreted large amounts of gastric juice at this time though no food was offered.

The psychic secretion in man

In man, the cephalic phase causes the secretion of from 50 to 150 cc. within 20 minutes (Ivy). Richet observed long ago that in a subject who had suffered esophageal stricture and into whose stomach an artificial opening (fistula) had been made for feeding purposes, secretion of gastric juice occurred upon the entrance of food into the mouth. Within recent years Carlson has carried out extended observations upon a subject who had had a similar operation performed for closure of the esophagus resulting from the ingestion of a corrosive in childhood. This subject therefore was already prepared, like Pavlov's dogs, for sham feeding, the only difference being that there was no opening in the neck, it being necessary to

spit out the food after chewing it. All the findings of Pavlov were, in the main, confirmed in the case of this subject. The influence of appetite or the desire for the food was particularly well brought out. The subject especially enjoyed the dessert, and the curve of gastric secretion showed the most pronounced rise when sweets or fruit, such as oranges, were chewed. The secretion, however, did not last for as long as in Pavlov's experiments, but commenced to decline as soon as the stimulation of the taste buds had ceased (fig. 187). Nor did the mere sight or smell of food (conditioned stimulus) evoke a response except when in one instance the subject was sent from the laboratory to select his meal from a near-by cafeteria. In this instance there was a very definite response to the sight and smell of the food. Several other observers have reported the existence of definite conditioned reflexes for gastric secretion in man.

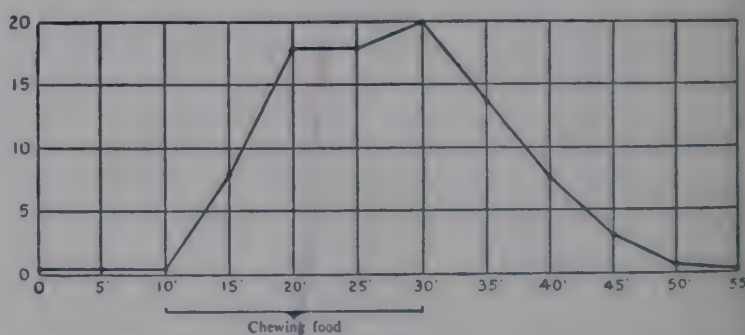


FIG. 187. Typical curve of secretion of gastric juice collected at 5-minute intervals during the mastication of palatable food for 20 minutes. The rise in secretion during the last 5 minutes of mastication is due to chewing the dessert (fruit) for which the person had an especial fondness. (After Carlson.)

The psychic effect upon gastric secretion has been demonstrated also by Bennett and Venables upon subjects during hypnosis. A suggestion made to the subject that he was eating some savory morsel of food called forth a secretion of juice. The suggestion of nauseating substances inhibited secretion. Psychic influences of an inhibitory nature have also been demonstrated by Hawk and associates who found that worry and anxiety retarded digestion. A meal disgusting in appearance and foul smelling (indol was scattered over the table) had a similar effect.

The application of these experimental results to dietetics is obvious. Foods agreeably flavored and attractive in appearance, impressions received from a meal prepared in a pleasing way, and, probably also, sensations aroused by the surroundings yet not directly concerned with the food itself, have all an effect upon gastric secretion. The impulse which guides the gourmet is sounder physiologically than that which impels the glutton.

The question of calories and the relative digestibilities of the various foodstuffs should not be allowed to obscure the psychic element entirely in these matters, for the "delights of the table" have true digestive value. These facts are expressed in the words of Pavlov "appetite spells gastric juice" or in the hospitable words of Macbeth "Now good digestion wait on appetite and health on both." Custom seems to have discerned this truth, for it has decreed that the meal shall begin and end with the more strongly flavored and appetizing morsels.

THE GASTRIC PHASE. THE SECRETION OF GASTRIC JUICE UPON THE ENTRANCE OF FOOD INTO THE STOMACH

When food is present in the stomach the secretion of gastric juice continues for a much longer time than can be accounted for by the psychic secretion. The factors concerned in this secretory phase must now be considered. In the first place, "What is the nature of the adequate stimulus? Is it mechanical—the mere contact of the food with the gastric mucosa? Or is it chemical?"

(a) **MECHANICAL STIMULI.** Pavlov demonstrated, apparently quite conclusively at the time, that mechanical stimulation of the gastric mucosa was entirely without effect upon the secretion of gastric juice. A glass rod having its tip covered with blue litmus paper remained unaltered in color when rubbed vigorously over the mucosa of the stomach. It was wetted by alkaline mucus but there was evidently no secretion of acid. Streams of sand when blown with considerable force against the mucosa so as to cause a more diffuse stimulation were also ineffective. More recently, however, Ivy and Farrell have shown that some degree of glandular excitation is caused by mechanical stimulation—particularly by the application of a distending force. There is an unusually long latent period and this is probably the reason that the effect was not discovered previously. The amount of juice secreted is, however, not great and, therefore, this type of stimulus cannot be wholly or even largely responsible for the flow which food induces by its presence within the stomach.

(b) **CHEMICAL STIMULI.** It was noted by Pavlov that certain articles of food such as bread and meat, which could not differ to any significant degree from one another in their physical effects upon the gastric mucosa, produced, nevertheless, greatly different secretory responses. Bread introduced through a fistula into a stomach that had been thoroughly dried of all residual juice,

and with the vagus nerves cut (in order to eliminate the psychic secretion), caused no excitation of the glands. Meat, on the other hand, under the same conditions, evoked an abundant flow of juice. The contrary results in the two instances must have been due it was argued, to chemical differences between the respective foods. The adequate stimulus was evidently chemical in nature and dependent upon substances contained in the meat. The various constituents of meat—its salts, water, protein and extractives—were then each investigated in turn for their secretagogue effect. Each was introduced into the main stomach, while the miniature stomach was observed for any signs of secretion.

With the exception of the *extractives* none of these components of meat had any pronounced effect. The *ash of meat* was without any effect whatever. *Water* caused a slight secretion (Reh-fuss has shown that water causes a much greater excitation in the human stomach than Pavlov reported for dogs). *Protein* itself, as in egg white, when the effect of its contained water was taken into account, appeared to be quite inert. Meat broths, meat juices and commercial extracts, such as Liebig's, all of which are rich in the watery extractives of meat, elicited a copious secretion.

Not only meat extractives but the *products of protein digestion*—*proteoses* and *peptones*—were equally powerful.

Having determined the specific stimulants for the gastric phase of gastric secretion, namely meat extractives and the products of peptic hydrolysis, the next question to be answered is "Through what mechanism do these substances act?" There are several possibilities. They might conceivably act (1) by direct stimulation of the gland cells; (2) through the stimulation of the afferent nerves in the gastric mucosa, thus bringing about secretion through a central reflex; (3) through their absorption into the blood stream, and their carriage therein to the glands; (4) through the local nerve plexus in the gastric wall, or, finally (5) by the liberation of a hormone from some part of the gastric mucosa which would then serve as the ultimate excitant.

The first two of these possibilities are ruled out as primary factors and (3) and (4) are improbable because of the following observations. Excitation of the glands of the miniature stomach occurs when the stimulating substances are placed in the main stomach. Injection of the materials intravenously causes a relatively small secretory response. The secretion occurs after the stomach has been completely isolated from the central

nervous system. The fifth possibility remains to be considered.

A consideration of a hormonal mechanism as responsible for the gastric phase.

The gastrin theory

In 1902 Bayliss and Starling discovered a hormone (secretin, p. 451) in the upper part of the small intestine which had a very powerful effect upon the secretion of pancreatic juice. The discovery of this substance led Edkins a few years later to search for one of a similar nature which might be concerned in the control of gastric secretion. He found that when the pyloric mucosa was ground up and extracted with some of the stimulating substances mentioned above, notably peptones, or with glucose or hydrochloric acid, the extract had a powerful secretory effect when injected intravenously. A simple watery extract was ineffective. Injection of the substances themselves directly into the blood stream was also incapable of causing secretion. Edkins gave the name *gastrin* to the undetermined principle in the active extracts. The conclusion drawn from these results was that gastrin, formed during normal digestion through the action upon the pyloric mucosa of substances derived from the food, was absorbed into the blood stream, and upon reaching the fundic glands excited them to activity.

As a result of later work (Koch, Luckhardt and Keeton) it was found that pyloric extracts were not specific but in common with other tissue extracts contained a secretagogue principle. This observation apparently deprived Edkins' results of any physiological significance in so far as gastric digestion was concerned. Popielski had, in 1920, demonstrated that histamine, which may be isolated from various tissues, was a powerful stimulant to gastric secretion. It was therefore suggested that the active principle in pyloric extracts (*gastrin*) was simply histamine. This view has been amply substantiated. Histamine is a constituent of pyloric extracts; and Sacks, Ivy and collaborators found that if the pyloric tissue were incubated with histaminase (the histamine-inactivating enzyme) before extraction, the preparation had no secretagogue action. This observation has been confirmed by Gavin, McHenry and Wilson who have also shown that in the dog, the tissue of the body of the stomach is richer in histamine than that of the pylorus and that 80 per cent of the total histamine content of the stomach is to be found in the former situation.

Extracts of the fundus (body) have also a great secretagogue action than have pyloric extracts.²

On the other hand, it has been shown definitely by Ivy and Farrell that an excitatory substance of some sort is actually carried in the blood stream during digestion to the glands of the fundus. These observers in a three-stage operation upon a dog, isolated completely a portion of the fundus and transplanted it into the subcutaneous tissue of the abdomen. After the operation, no nervous or direct vascular communications between the two sections of the stomach remained. When the animal was fasting, the transplanted pouch secreted a little mucoid fluid containing a small amount of combined acid, but no free acid. After the animal had been fed and digestion had proceeded in the main stomach for from 2 to 5 hours, an increase in the volume and in the combined acid of the juice secreted by the transplanted pouch occurred; in some instances free acid appeared.

The results of later experiments by Gregory and Ivy on dogs indicate that the blood-borne substance is a hormone. They created two completely denervated stomach pouches. One pouch consisting of a small part of the fundic region was transplanted (transplanted pouch) to the subcutaneous tissue of the mammary gland. The rest of the stomach (main pouch) was separated from the esophagus and duodenum which were then anastomosed. Perfusion of the main stomach with liver extract, which is a potent source of secretagogues, caused the secretion of free acid from both pouches. Mechanical stimulation (distension) of one pouch caused secretion from that pouch but not from the other. It is evident that, since the main pouch and the transplant are connected only through the general circulation, the action of the secretagogues is followed by the passage into the blood of a substance which stimulates the gastric glands, but that mechanical stimulation is incapable of initiating such a mechanism. When the animal was given a meal of bread, meat and milk (which passed directly into the intestine) both pouches secreted free acid in fairly large amounts for several hours.

² The term *secretagogue* may be applied to any substance which excites secretion no matter by what mechanism the secretion is ultimately brought about. The term *hormone* will be used to indicate a secretory extract which is absorbed from the cavity of the stomach or intestine and carried in the blood stream to the gastric glands. The use of the word *hormone* will be confined here to any secretory substance secreted in the gastric or intestinal tissue and conveyed to the glands in the blood stream.

These results still left unsettled the question of the nature—humoral or hormonal—of the food-borne substance, that is, whether the secretagogues themselves were absorbed into the blood stream or whether they acted upon the gastric mucosa to produce a new stimulating substance or to cause a preformed substance to be liberated into the circulation. Anesthetizing the mucosa of the main pouch with procaine prevented the action of the secretagogues in the main stomach as well as in the transplanted pouch. Yet after anesthetization of the transplanted but not of the main pouch, secretagogues exerted their usual effect when introduced into the latter. This proves that the anesthetic does not paralyze the gland cells. Nor does procaine prevent the action of the blood-borne substance formed during normal digestion, once it has entered the blood stream, because secretion from the anesthetized main pouch occurs after the animal has been fed and food has entered the intestine. These experiments pointed definitely to a hormonal mechanism, although the possibility remained that the secretagogues themselves are humoral agents, the absorption of which had been depressed by the anesthetic. In experiments with other secretagogues such as histamine and ethyl alcohol, no evidence of such an effect of the anesthetic was secured.

The pyloric region has been thought by several to be essential for the production of the gastric hormone, but, in other experiments of Gregory and Ivy, pouches from which the pylorus had been removed gave essentially the same response when secretagogues were introduced into the remaining part of the stomach. The pyloric region, therefore, appears to have no special function in this regard.

THE NATURE OF THE GASTRIC HORMONE. The question now arises whether or not the gastric hormone, i.e., the substance liberated into the blood stream when food enters the stomach, is identical with the active principle in pyloric extracts (gastrin). In other words, is histamine the gastric hormone? This question cannot at present be answered definitely. That the activity of pyloric extracts is destroyed by histaminase does not settle the point, for (a) this enzyme has not been proved to be absolutely specific for histamine and (b) it may possibly be that a gastric hormone, not identical with histamine, exists but has not been obtained by extraction. The fact that anesthetizing the mucosa prevents the effect which follows the placing of food in the stomach does not the effect resulting from the injection of

gastrin would seem to indicate that the two substances are not identical. It is conceivable, however, that these drugs merely interfere with the formation of the hormone (whether it be histamine or some other substance) and yet have no effect upon the absorption or action of any hormone which had already been formed in the mucosa. The observation that the juice resulting from histamine injections differs from normal gastric juice suggests, again, that the gastric hormone is not simply histamine. According to Babkin and his associates the gastric juice formed by the stomach of the dog as a result of the injection of histamine or of purified gastrin, though possessing a high acidity, has a low concentration of pepsin. Babkin also points out that though histamine is very readily extracted by acids, hydrochloric acid placed in contact with the pyloric mucosa does not stimulate gastric secretion; a 0.5 per cent solution is actually inhibitory (Alley). Moreover, histological examination of the gland after histamine injections shows an effect confined to the acid-producing cells; in contrast to the appearance after vagal stimulation, the peptic cells were entirely unaffected (Bowie and Vineberg). It is stated, on the other hand, that pepsin is present in fairly high concentration in human gastric juice produced by histamine injections (Bloomfield and Pollard); but in observations upon the human subject the possibility of the enzyme secreted prior to the injection having been simply washed out of the tubules by the secretion of the parietal (acid) cells is difficult to exclude. Indeed, evidence that the high concentration of pepsin was due to washing out of preformed ferment has been obtained by Teby who found that when histamine was administered repeatedly to patients the peptic activity of the juice declined progressively with each successive injection. Bucher and his associates, on the contrary, observed that in animals the pepsin concentration actually increased when repeated small doses of histamine were administered.

The foregoing is a summary of the main experimental facts which argue against histamine being a gastric hormone. The question, however, is very complex and cannot be answered definitely in the face of such conflicting results. But a fresh light has been thrown upon it by the observations of Grossman, Woolley and Ivy who have pointed out that the gastric hormone, which has been demonstrated experimentally and which acts presumably during normal gastric digestion, causes the secretion of a juice low in peptic power. It is also recalled that a hormonal mechanism

for the secretion of pepsin such as may follow vagal stimulation or pilocarpine administration has never been shown to exist. These investigators found that liver extract, which has a powerful secretagogue effect, causes the production of a juice closely similar to that due to histamine, namely, of low peptic power. They conclude that the gastric hormone which has been demonstrated to cause this type of secretion *may be* histamine and that the high concentration of pepsin in the gastric juice secreted under normal circumstances is brought about by some other mechanism.

We can, at least, safely say this much with regard to histamine, or indeed of any known gastric hormone, that in eliciting a secretion of pepsin it is much inferior to nerve stimulation.

It has been suggested that histamine may play a rôle in gastric secretion somewhat different from that just discussed, namely, by serving as a chemical mediator of the vagal control of the parietal cells, i.e., as a "local hormone" liberated by the vagal nerve endings. The facts that histamine is present in the gastric juice, that its concentration in the juice is increased by vagal stimulation and that its content in the body of the stomach is much higher than that of the pyloric region accords with this possibility.

THE INTESTINAL PHASE OF GASTRIC SECRETION

The products of gastric digestion upon entering the duodenum act as chemical excitants to gastric secretion. If a meal of bread and milk is fed to an animal, as prepared in Gregory and Ivy's experiments, a secretion from both the main stomach pouch and the transplant commences within about 2 hours and continues for from 3 to 9 hours. It appears that the mechanism is hormonal in nature and similar to that which stimulates secretion during the gastric phase of digestion, split digestive products acting as secretagogues. Mechanical stimulation of the intestine, as by distension, is ineffective, and, as mentioned on page 435, the application of procaine to the gastric mucosa does not abolish the response. Various substances placed directly in the duodenum, e.g. water, meat extracts, albumoses and peptones, magnesium sulphate, saponin, soaps, etc., have been shown to excite the glands of an isolated stomach pouch. Crider and Thomas found that when the duodenal contents were drained away through a fistula, the response of the gastric glands to a meal was only a third of the normal value. Gastric secretion is inhibited by fat or by acid in the duodenum.

THE INHIBITORY EFFECT OF FAT UPON THE GASTRIC GLANDS

Fat, after it reaches the intestine, inhibits gastric secretion. Later, secretion is stimulated; the mechanism of this secondary stimulation is not clear; it is not due, apparently to soaps. The inhibitory effect of fat is sufficiently powerful to antagonize the psychic phase of gastric secretion and the stimulant action of histamine.

The motility of the stomach is also depressed (p. 485) by fat; hunger contractions are inhibited. The manner in which fat exerts its inhibitory effect upon secretion has been clarified by the experiments of Ivy and of Lim and their associates. A hormone (chalone, p. 670) is responsible. Lim found that fat placed in a denervated isolated pouch was followed by inhibition of secretion in the main stomach. The inhibitory influence, he concluded, was not due to the absorbed fat itself since the effect was not abolished by draining the chyle to the exterior and so preventing absorbed

TABLE 32*

	SECRETION TOTAL	ACID CON- CENTRATION	PEPSIN CON- CENTRATION
Meat.....	High	High	Medium
Bread.....	Medium	Low	High
Milk.....	Low	Medium	Low

* Modified from Carlson.

fat from entering the general circulation. Fat reduces the quantity and acidity of the juice but depresses especially the peptic power. Ivy and his associates have extracted a substance from the intestinal mucosa which, when injected, produces the characteristic inhibitory effect upon gastric secretion and motility. This material which has been named *enterogastrone* is free from depressor (vasodilator) activity and does not contain secretin (p. 451) nor cholecystokinin (p. 475).

It is capable in maximal doses of causing complete suppression of secretion for from 1 to 5 hours and of gastric motility for 30 minutes. In smaller dosage, it reduces acid and peptic secretion. The effect upon pepsin secretion is not observed after vagal denervation. There is some evidence that the effect upon gastric motility is due to a principle closely associated with but distinct from that which inhibits secretion.

A substance known as *urogastrone* and having effects similar to enterogastrone upon gastric secretion and motility has been extracted from

normal urine by Gray and his associates. Urogastrone was thought at first to be most probably excreted enterogastrone but certain differences have since been demonstrated which indicate that they are separate and distinct substances. Pepsin inactivates enterogastrone but has no effect upon urogastrone.

THE ADAPTATION OF THE QUANTITY AND QUALITY OF THE GASTRIC SECRETION TO THE TYPE OF FOOD. It has been shown by Pavlov and Khizhin that the juices secreted for the three foodstuffs, bread, meat and milk, respectively, differ characteristically from one another, both in quantity and digestive power. Indeed the juice secreted for each type of food is, according to Pavlov so specific and suited to the digestion of the particular foodstuff which calls it forth, that it is possible to predict the character of the juice which will be secreted when a given type of food is fed. He therefore speaks of "meat," "bread" and "milk" juice, respectively. The juice secreted for *meat*, for instance, was found to be greatest in quantity, but intermediate in digestive power between those formed for bread and for milk. *Bread juice* possessed the highest peptic power (about double that of meat juice) but was intermediate in amount. It was suggested that the high ferment value was an adaptation furthering the digestion of the more resistant vegetable proteins. *Milk juice* was both scanty in amount, and poor in peptic power during the first four hours of secretion. The low values of the juice secreted for milk was ascribed to the inhibitory effect of the milk fat. The acidity is highest in meat and lowest in bread juice. In the case of the human stomach meats are recognized to be, as compared with other foods, the most powerful stimulants of acid production. (See table 32.)

The acidity of the gastric juice as collected from the stomach in many instances shows a tendency to vary with the rate of secretion by the fundic glands; when their rate of secretion is slow the juice will be diluted to a greater extent by mucous fluid than when the rate is rapid. It was Pavlov's view that variations in acidity are due entirely to changes in the rate of total secretion into the stomach and that *the acidity of the juice as secreted by the parietal cells is constant* (p. 424). The reverse relation holds between rate of secretion and pepsin concentration, the latter becoming reduced as the secretion rate increases. These relationships are dependent upon the fact that the acid secreted by the parietal cells makes up the bulk of the fluid of the juice. Juice of large volume is therefore highly acid, that of small volume contains a relatively high concentration of pepsin and alkaline mucus. Such relationships hold true, however, only when the same type of secretory stimulus is employed and its intensity varied. When, however, the type of stimulus is altered it appears that the acidity or peptic activity of the juice may vary independently of the rate of secretion. That is, a slow or rapid secretion rate may

be associated with either a low or high acidity, and similarly with the pepsin concentration. Furthermore, the proportions of the three main constituents of the juice, acid, pepsin or mucin, can vary independently of one another. Alley found, for example, that haddock muscle prepared in various ways caused qualitative differences in the juice secreted. Baked haddock increased the quantity of juice and the concentrations of pepsin and mucin. Smoked haddock stimulated the acid production and increased the quantity but the juice was poor in mucin and pepsin. It has been mentioned above that fat exerts a much greater depressing effect upon the peptic power of the juice than upon its acidity or quantity. Histamine provokes the secretion of a highly acid juice containing little or no pepsin, while insulin (p. 438) stimulates chiefly the peptic cells. The different elements of the gastric glands, parietal, peptic or mucous cells, are therefore not necessarily excited to the same extent by a given stimulus; and different types of stimulus affect the respective secreting elements in varying degree.

THE EFFECTS OF VARIOUS CHEMICALS AND DRUGS UPON GASTRIC SECRETION

Alkalis in general have been held to exert a depressing effect upon the secretion of gastric juice. Sodium bicarbonate, for instance, a favorite ingredient of digestive mixtures was investigated by Pavlov in dogs and found to be definitely inhibitory. This observation has been confirmed by Farrell, though others find that the inhibitory effect does not occur unless the dose is excessive, and that in small repeated doses it augments the secretion (Boyd). This seems to be true also of other alkalis, large doses depress but small doses, especially if repeated, may augment the flow of juice, thus alkaline drinks are mildly stimulating. Nor does the inhibitory effect of large doses persist after their discontinuance; on the contrary, hypersecretion not uncommonly follows. The value of alkalis in gastric disorders depends chiefly, however, upon their antacid properties i.e., upon their ability to neutralize the acidity of the gastric contents.

The various preparations of *bitters* are without any appreciable effect upon secretion unless they contain *alcohol*. The latter has a pronounced secretagogue action, causing the secretion of a juice of high acidity and rich in mucin. It is possible that alcohol exerts its secretory action through the liberation of histamine, for it has been shown that the histamine output of the perfused lung of the guinea pig is increased by the addition of alcohol (2-6 per cent) to the perfusion fluid. *Acids* depress gastric secretion which is completely inhibited by the introduction into the stomach

of a 1 per cent solution of hydrochloric acid (p. 441). *Condiments* have little direct effect, but act indirectly in adding flavour to the food, stimulating the taste buds and thus encouraging the psychic secretion. *Histamine* is one of the most powerful stimulants of gastric secretion (p. 442). Histamine liberated within the body e.g. in dermographism (p. 268) or even by the immersion of the hand in cold water at a temperature of 10°C. causes a detectable secretory response within 15 minutes. *Liver extract* (used in treatment of pernicious anemia) is also a powerful secretory excitant. *Insulin* (through its hypoglycemic effect on the vagus center), *acetylcholine* (usually), *mecholyl* (*acetyl-β-methylcholine chloride*), *pilocarpine* and *nicotine* are secretory stimulants, while *atropine* is a depressant. Atropine does not, however, inhibit the secretagogue action of alcohol and only partially prevents the effect of histamine. *Smoking* causes an increase in gastric acidity which is not due, entirely at any rate, to nicotine. *Morphine* after a brief period of inhibition stimulates gastric secretion.

THE EFFECTS OF OPERATIVE PROCEDURES UPON GASTRIC SECRETION

In dogs, partial gastrectomy (excision of the pylorus and anastomosis of the gastric stump to the duodenum) is followed by a pronounced reduction in the *quantity* of juice secreted by the fundic glands but no change occurs in the *concentration* of acid. The total acid secretion is, therefore, reduced to $\frac{1}{2}$ or $\frac{1}{3}$, (see Wilhelmji and associates). Mucous secretion is increased, and combining with the acid thus further reduces the free acid concentration of the gastric contents. Partial gastrectomy, accompanied by section of the gastric vagi, results in a profound reduction in acid secretion in response to a test meal; histamine, however, still causes a well-marked secretion.

Transplantation of a section of jejunum, with its blood supply intact, into the wall of the stomach has been shown by Stefko and his colleagues to result in a reduction of the free and combined gastric acidity during fasting and to reverse the response to histamine.

ANALYSIS OF THE STOMACH CONTENTS—TOTAL ACIDITY—FREE ACIDITY

During digestion the hydrochloric acid in the stomach exists in two forms—a smaller part combined with the protein of the food, regurgitated duodenal secretions and mucous—*combined acid* and a much larger part present in the free state—*free acid*. The sum of these

two, together with acid salts and any organic acids lactic etc. that may be present, is termed the *total acidity*. Meat and other protein-rich foods are more capable of combining with hydrochloric acid than are carbohydrates. When the hydrochloric acid is absent or falls to a low level organic acids, as a result of the fermentative processes, tend to be formed.

Samples of gastric contents are obtained for analysis by means of a Rehfuß tube. This is made of narrow flexible tubing fitted at one end with a metal tip possessing large perforations. The subject is instructed to swallow the tube slowly. To its upper end a syringe is attached, and by means of this the stomach contents are aspirated. This is done the first thing in the morning before food or drink has been taken. The healthy resting stomach secretes continuously and the fluid removed at this time (*residual juice*) under normal conditions amounts on the average to 50 cc. The total acidity of such a sample normally averages 30 units and the free acidity 20 units (see below). After the removal of the residual juice the gastric glands are excited to secrete by the ingestion of a *standard test meal*. Ewald's test meal is frequently employed and consists of two ordinary slices of toast (35 grams) and 8 ounces (250 cc.) of weak tea without milk. Others give a pint of thin gruel (Boas meal). Dilute alcohol (50 cc. of a 7 per cent solution) or an injection of histamine is also employed for stimulating gastric secretion. When the test meal is used a specimen of gastric contents (10 to 15 cc.) is removed 15 minutes after the meal has been swallowed, and during the succeeding 2½ hours at 15 minute intervals. Finally, the gastric contents are completely removed. Determinations of the free and the total acid are then made upon each sample and the corresponding acidity curves constructed (pp. 439, 440). The tube remains in position throughout the test. It was at one time the custom to make a single analysis 1 hour after the meal and to draw conclusions concerning gastric function from the results of this. But, since the acidity is continually changing, the construction of a curve from the results of analyses made at short intervals is the only logical procedure. This is known as the *fractional method of gastric analysis*, and was introduced by Rehfuß and his collaborators.

Chemical tests

QUALITATIVE. (a) *Free hydrochloric acid*. A drop of Topfer's reagent which consists of a 0.5 per cent solution of dimethyl-amino-azo-benzol is added to a cubic centimeter or so of the gastric contents. This reagent gives a red color at a pH below 3.0, that is in the presence of free HCl. It is not quite specific for it may react to high concentrations of organic acids. Gunsberg's test is more delicate and is quite specific for free HCl, giving no color change whatever with organic acids. Two drops of the reagent (1 gm. vanillin and 2 gm. phloroglucin in 30 cc. of 95 per cent alcohol) are added to 5 cc. of filtered gastric contents

in a porcelain dish. The mixture is heated over a flame with care to avoid charring. A red or orange discoloration at the drying margin of the solution is taken to indicate the presence of free HCl.

(b) *Lactic acid*. When free HCl is absent from the gastric contents (anacidity, p. 740) fermentation is likely to occur with the production of organic acids, particularly lactic. The latter is detected by means of Kelling's test—a modification of Uffelmann's. Two drops of 10 per cent ferric chloride are added to a test-tube full of distilled water. The solution is divided between two test-tubes in equal portions. A few drops of filtered gastric contents are added to one tube; a lemon yellow color appears if lactic acid is present. The solution in the other test-tube serves as a standard for comparison. The gastric contents may contain other substances which give the test and, for this reason, it is preferable to take up the lactic acid with ether, evaporate to dryness and dissolve the residue in water. The test is then applied to the aqueous solution.

QUANTITATIVE. (a) *Free hydrochloric acid*. Five cc. of strained gastric contents are diluted with 25 cc. of distilled water. Three drops of Topfer's solution are added as an indicator. The sample is then titrated with N/10 NaOH to pH 2.8 as indicated by a salmon-pink color.

(b) *Total acidity*. After noting the reading of the burette and estimating the free acid, three drops of phenolphthalein solution are added to the specimen and the titration with sodium hydroxide continued until the solution turns a definite pink.

In precise experimental work, Hollander recommends the use of bromphenol blue as indicator for free acidity, the titration being carried to pH 3.5, and phenol red for the total acidity, the end point being at pH 7.

The results of these determinations are expressed in "clinical units" i.e., the number of cubic centimeters of decinormal sodium hydroxide solution which would be required to bring 100 cc. of stomach contents to the end-point in each case (the actual figures for the free and total acid are multiplied by 20, since the volume of the specimen was 5 cc.). The total quantity of alkali required gives the value for the total acid; the first titration gives the free acid. The *percentage* of free HCl is obtained by multiplying the number of cubic centimeters of alkali required for neutralization by the factor 0.00365 (see graph, fig. 188).

(c) *Combined hydrochloric acid*. The difference between the value for the total acid and that for the free acid ($b - a$) gives the value of the combined acid plus that of any organic acids which may be present.

Estimation of peptic power

The earliest method of determining the peptic activity of a sample of gastric juice is that introduced by Mett in 1889. Egg white is drawn into a glass tube of 1 mm. bore and a few inches long. The albumin is coagulated by placing the tubes in water at a temperature of 85°C. and leaving them there until the

water has cooled. The tube is then broken into sections about an inch long, two or three of which are immersed in the gastric juice diluted 1 to 15 with N/20 HCl and incubated at a temperature of 37°C. for 24 hours. After this time the length of the column of digested albumin at each end of the tubes is measured in millimeters under the low power of the microscope and the average of a number of measurements taken. The peptic power of the sample is expressed in accordance with Schutz's law which states that the amount of proteolytic enzyme present is proportional to the square of the number of millimeters of digested albumin. Therefore, if the average length of the digested columns is 2.5 mm. the peptic power of the undiluted juice will be $2.5^2 \times 16 = 100.0$. This is the average normal value.

In the Gilman and Cowgill method, as modified by Gates, the peptic activity is determined from the rate at which the gelatin coating on a piece of photographic film is digested. The reduction in the opacity of the film is compared with a standard. Anson's method utilizes hemoglobin as the substrate. After the juice has acted upon the hemoglobin for 10 minutes, the undigested protein is precipitated with trichloroacetic acid and removed by filtration. The quantity of protein split products, which is a measure of peptic activity, is estimated colorimetrically after the addition of phenol reagent.

Determination of gastric secretory function

It is becoming more and more evident that the methods of gastric analysis as carried out in the time-honored fashion are inadequate as a means of gaining knowledge of the secretory activity of the stomach. They measure the acidity of the gastric contents and, therefore, frequently give false information or equivocal results concerning *secretion*. The acidity of the gastric contents removed after a test meal depends not only upon the secretion by the gastric glands but also upon the degree to which the secretions have been diluted by the fluids of the test meal still remaining in the stomach. It is not possible to know how much of the meal has left the stomach by the time the samples are withdrawn, unless there be added to it some soluble substance which is neither absorbed nor destroyed in the stomach and can be easily detected. Phenol red may be used for this purpose. The proportion of the gastric contents which has been secreted can then be determined and by dividing the value for the total acidity by the volume of the secretions, the acid concentration of the gastric juice itself (which contains a variable proportion of mucin) can be estimated. Furthermore, since the acid concentration of the parietal cell secretion is constant, it is possible to determine the proportions of acid and non-acid secretions in the juice.

The test meal of bread or toast and tea usually employed is unappetizing and too weak a stimulus to all phases of gastric secretion nor can alcohol or histamine rightly be considered a normal physiological

secretagogue. Liebig's test meal, consisting of a 2 per cent solution of Liebig's meat extract, contains potent and physiological secretagogues and is probably the nearest approach to the ideal test meal. The histamine test (p. 442) is valuable as a means of distinguishing true from false anacidity.

THE ISO-SECRETORY OR NORMAL CURVES OF GASTRIC ACIDITY

If in a normal person the free and total acidities of the gastric contents be determined every 15 minutes for a period of from two to three hours after the ingestion of a test meal, and the results plotted with time along the base line and HCl percentages in the vertical axis, a curve is obtained as

the great bulk of normal persons; but the gastric acidities show very wide individual variations in health, being influenced markedly by age and sex. The average free and total acidities (after a test meal) in young healthy males are about 40 and 65, respectively (see figs. 189 and 190). They are somewhat lower in females. They are also lower in children, the adult level being reached at about the age of 20 years. In men after 30 years and in women after 50 years a progressive decline in acidities (total and free) occurs and the incidence of anacidity and of subacidity (p. 442) increases sharply. A high normal value for gastric acidity is regarded by some as an index of physical fitness.

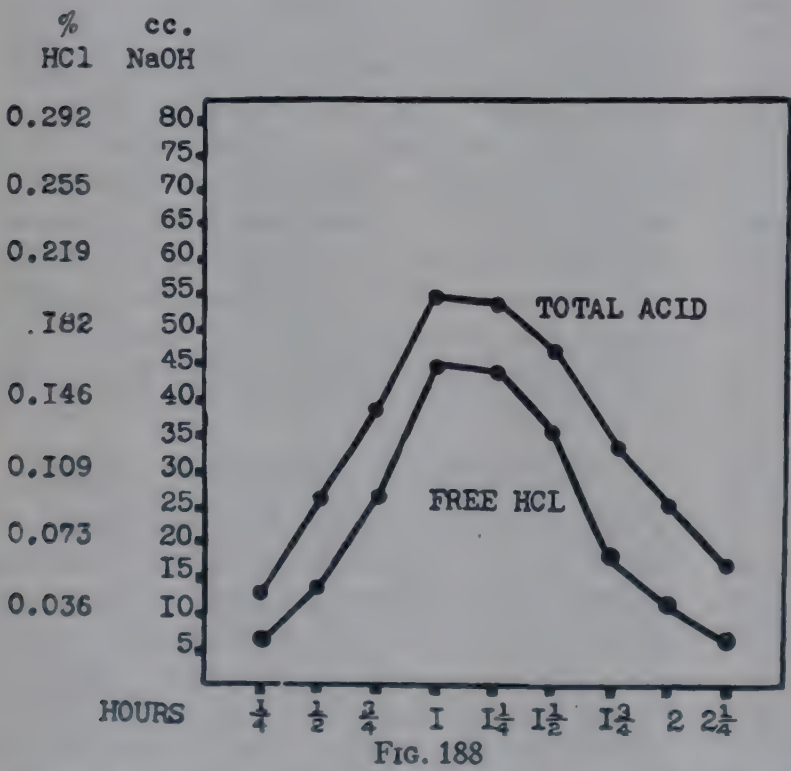


FIG. 188. Normal curves of gastric acidity following a test meal. (Redrawn from Maclean.)
FIG. 189. Normal standards. The shaded areas represent the limits within which lay 80 per cent of the data for free and total acid at the different ages. The heavy lines represent modes. (After Vanzant, Alvarez and associates.)

shown in figure 188. The curve for total acidity commences to rise a short time after the meal, and about 1 hour later reaches a maximum which varies from 35 to 70 in different persons. The curve maintains its maximal height for half an hour or less and then commences to decline reaching the resting level again in from 2 1/2 to 3 hours after the ingestion of the test meal. The curve of free acidity runs parallel to, but at a lower level than that for the total acidity, the values ranging in different normal persons between 20 and 40 (0.07 to 0.15 per cent). Values are much higher after foods, such as meats, which stimulate gastric secretion more powerfully, averaging from 80 to 120 for total and from 60 to 100 for free acidity.

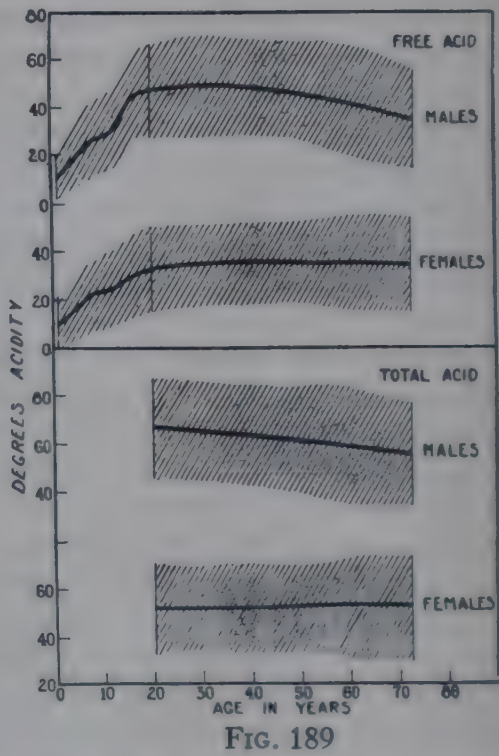
The figures given above represent the range of

the level tending to be low, it is said, in persons of sedentary habits and poor muscular development.

THE REGULATION OF THE ACIDITY OF THE GASTRIC CONTENTS

The normal acidity curves, as we have seen, reach their maxima in about an hour and then commence to decline. The fall in the acidity of the gastric contents has been attributed by various authors to the following factors.

- (1) Reduction in the concentration of acid in the gastric juice.
- (2) Reduction in the total volume of juice as a result of the cessation of the psychic stimulation and gradual reduction in the secretagogue action



of the food as gastric and intestinal phases subside.

(3) Evacuation of the stomach.

(4) Reduction in free acidity of the gastric contents by saliva, food derivatives and by the alkaline mucous secretion of the pyloric portion of the stomach.

(5) Neutralization of the juice by the regurgitation of alkaline duodenal fluids—especially pancreatic juice—into the stomach.

With regard to the first factor, some authors (Rosemann, and Maclean and Griffiths) have thought that the fundic glands could secrete chloride ions in combination either with Na or H ions, i.e., as NaCl or HCl, the proportions of acid and of neutral chloride in the juice being determined by the H ion concentration of the gastric contents, a rise in their acidity causing automatically a larger proportion of chlorine to be secreted as the neutral salt. Bolton and Goodhart failed

secretion. The cephalic phase remains unaffected by acid either in the stomach or duodenum. The inhibitory effect of acid appears to be mediated through a nervous mechanism rather than by a blood-borne agent.

The termination of the cephalic phase and the progressive weakening of the gastric and intestinal phases, as the food is evacuated from the stomach and absorbed from the intestine, are important factors in the decline of gastric acidity.

Regurgitation of fluids from the duodenum has been considered an important contributory element in lessening acidity. The importance of this latter factor is, however, very questionable. That duodenal regurgitation occurs is an undoubted fact as is evidenced by the appearance of bile and trypsin in the stomach, especially in the later stages of digestion. Boldyreff in 1907 was the first to give duodenal regurgitation a prominent rôle in the regulation of gastric acidity. This observer maintained that normally a high acidity of the chyme issuing from the pylorus stimulated the secretion of pancreatic juice and set up antiperistalsis in the duodenum which carried the alkaline fluid into the stomach. The following observations, however, seem to show that duodenal regurgitation is a non-essential part of the mechanism controlling gastric acidity.

(a) Baird, Campbell and Hern observed in human subjects that the usual fall in gastric acidity occurred though the reflux of fluid from the duodenum into the stomach was prevented (duodenal contents removed by duodenal tube).

(b) McCann prevented regurgitation in dogs by separating the duodenum from the stomach and jejunum, and draining it into the lower part of the ileum. The stomach was then joined to the jejunum. The acidity curves of these animals did not differ from those of normal animals.

(c) Gastric acidity curves of isolated gastric pouches in dogs are essentially the same as those obtained from the intact human stomach.

(d) Shay, Katz and Schloss found that alkaline fluids introduced into the stomach caused a greater reflux from the duodenum than did strong acids. Water and weak acids were as effective as strong acids. These authors also pointed out that normally the juices secreted into the duodenum have a pH of around 7.2 or lower, and consequently, are not sufficiently alkaline to exert, in the quantities which are regurgitated, an important effect upon gastric acidity.

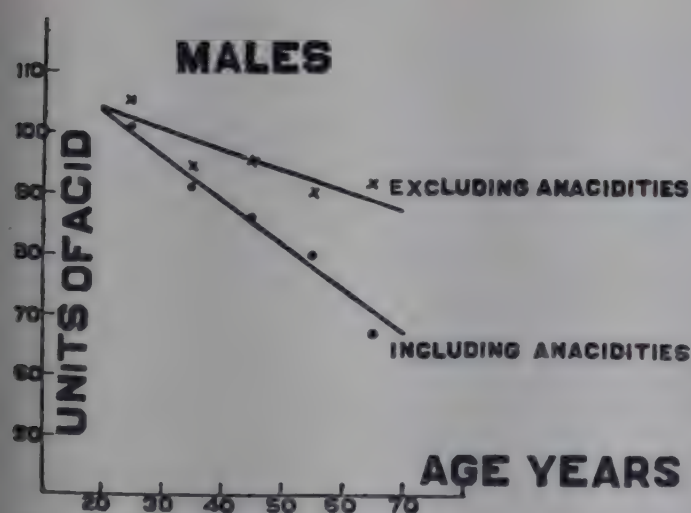


FIG. 190. Percentage decline of mean gastric acidity with advancing years (males). (After Polland.)

to obtain evidence in support of this view. They conclude that the main gastric factors bringing about the fall in acidity are, reduction in the quantity of the juice secreted by the fundic glands and evacuation of the stomach. Neutralization of the contents by the secretion of mucus was found to exert a minor effect, and only at a time when the secretion of juice was already greatly diminished. The original view of Pavlov that the acidity of the gastric juice as secreted by the glands remains constant has been confirmed by Hollander and is now widely accepted. It is apparently only the volume of the parietal secretion which varies. A rise in the acidity of the gastric contents automatically reduces the quantity of juice produced during the gastric phase of secretion. A high acidity in the duodenum also inhibits both the gastric and intestinal phases of

THE HISTAMINE TEST

As a test of gastric secretion the parenteral administration of histamine although not a normal stimulus has certain very definite advantages over the ordinary test meal: (a) Histamine evokes a maximum secretory response and is often able to evoke a response when the test meal fails to do so (see below). It is thus of value in distinguishing false from true acidity. (b) The response is not affected by conditions such as appetite and other psychic factors which influence the response to

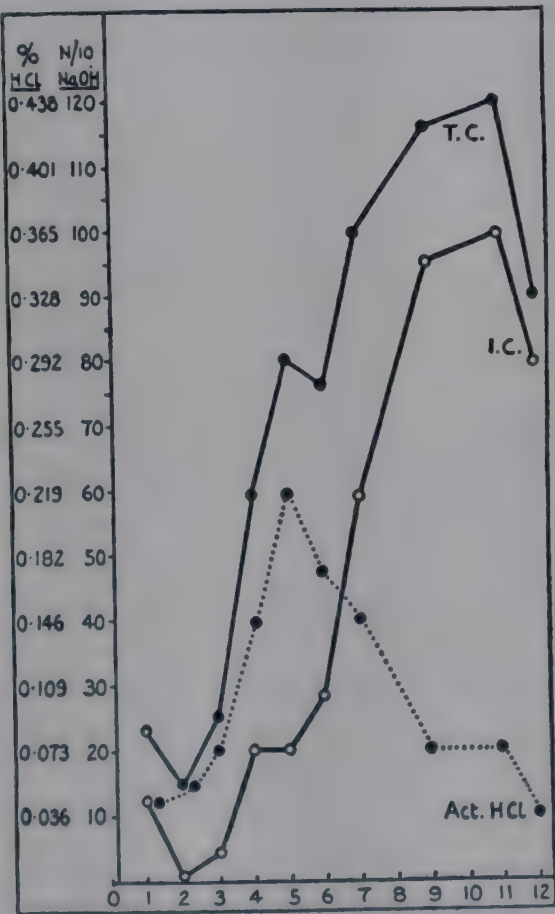


FIG. 191. Analysis of gastric contents at 15 min. intervals after a test meal. T.C., total chlorides; I.C., inorganic chlorides; Act.HCl., "active" hydrochloric acid (i.e., difference between total and inorganic chlorides). (After Bolton, slightly modified.)

the test meal. (c) The test meal and salivary secretion, which latter cannot be measured, add to the volume of the contents; it is therefore impossible to determine accurately the quantity of juice secreted. (d) Swallowed saliva and the test meal itself partly neutralize the acid. (e) In the histamine test the glands respond promptly, maximal acidity being reached within 20 or 30 minutes; so practically pure juice is obtained for analysis, neutralization factors and gastric evacuation exert a minimum influence. The test is usually performed the first thing in the morning with the subject fasting. In a subject of average weight about 0.25 mg. is injected.

HYPOCHLORHYDRIA (SUBACIDITY) AND ANCHLORHYDRIA (ANACIDITY)

When the stomach contents give values persistently below 20 "clinical units" (0.05 per cent for free HCl after test meals, the condition is spoken of as *hypochlorhydria* or *subacidity*. The complete absence of free HCl is referred to as *achlorhydria* or *anacidity*. Bennett and Ryle in a study of 100 healthy male subjects (medical students) found achlorhydria present in 4.0 per cent. In the general run of hospital cases without gastric disease or pernicious anemia 14 to 20 per cent show anacidity. It has already been pointed out that the absence of free hydrochloric acid from

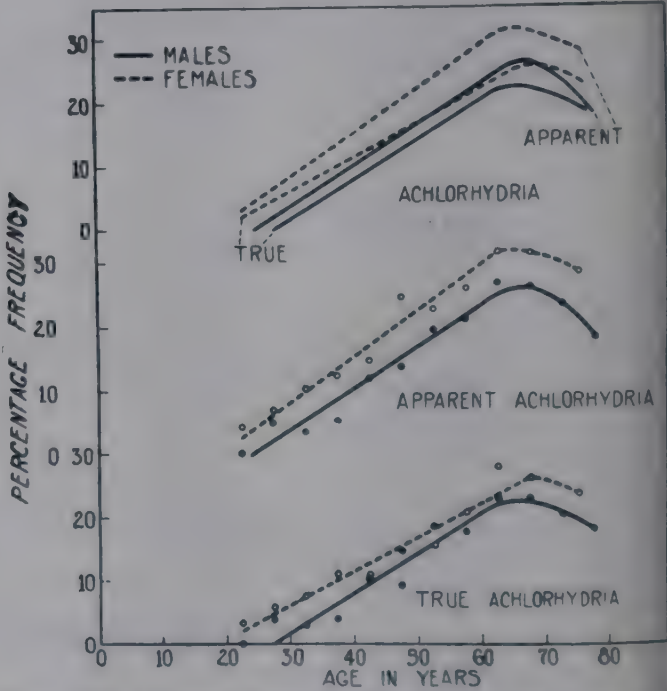


FIG. 192. Curves showing the relation between the incidence of achlorhydria and age. (After Vanzant Alvarez, and associates.)

the stomach contents may be simply the result of excessive neutralization, and not of the suppression of acid secretion. Again, there may be no secretion of acid after a test meal yet the glands respond to the more powerful stimulus of histamine: anacidity of this character is called *false* or *apparent anacidity*. The failure of acid to appear after the injection of histamine is referred to as *true anacidity*. The figures given above as reported by Bennett and Ryle for anacidity in healthy subjects as well as those given for hospital cases do not permit a distinction to be drawn between the two types of the condition, since test meals were used in the investigations. It is therefore impossible to say in what proportion of the cases true anacidity existed. The incidence of

true anacidity appears, however, to be less than 1 per cent in young healthy male subjects and not more than 1 or 2 per cent in the case of young healthy females.

In cases of anacidity the peptic concentration of the gastric juice through usually low is in some cases not far below the normal value—further evidence that the secretion of acid and of pepsin are governed by independent mechanisms. Complete absence of both acid and pepsin from the gastric contents is called *achylia gastrica*.

The incidence of anacidity, both apparent and true, shows a definite increase with advancing years up to the sixth decade. Alvarez, Vanzant and associates, in an investigation of a large series of patients without gastric disease, found it present in from 25 to 35 per cent between the ages of 60 and 70 years. Females showed a higher incidence than males. After the sixth decade some reduction in the frequency of the condition was observed (see figs. 189 and 192).

Anacidity in the majority of instances gives rise to no gastric symptoms and is compatible with perfect health. In some cases it is associated with flatulent dyspepsia and occasionally a persistent diarrhea (gastrogenous diarrhea) which is relieved by the administration of acid.

The following are the chief pathological conditions associated with anacidity;

(a) *Pernicious anemia*. Achlorhydria is a constant phenomenon (p. 64). Pepsin is also usually absent. Histamine is ineffective.

(b) *Carcinoma of the stomach*. There is anacidity in over 60 per cent of cases. It is due, according to Hurst, to the chronic gastritis which precedes and accompanies the growth. The anacidity may be either false or true.

(c) *Chronic gastritis* causes a gradual depression of the secretory function and may lead finally to its complete suppression.

(d) Hypochlorhydria or achlorhydria may also occur during *acute fevers*, in *malnutrition*, *gall-bladder disease*, *Addison's disease*, *sprue*, *acne rosacea* and *chronic arthritis*.

HYPERCHLORHYDRIA (OR HYPERACIDITY)

Hyperchlorhydria is also of common occurrence. About 5 per cent of healthy persons show the condition.

The free acid has a value of from 60 to 90 after a standard test meal, and may, instead of declining in the second hour, remain high or continue to rise. The high acidity of the gastric contents does

not mean that the juice as secreted by the gastric glands is excessively acid. So far as is known the normal maximum of from 0.5 to 0.6 per cent of hydrochloric acid in the gastric secretion is never exceeded. The high acidity of the gastric contents is due either to the secretion of an abnormally large quantity of juice (hypersecretion) or to impairment of the factors regulating gastric acidity (p. 440), e.g., failure of the secretion rate to become reduced during the second hour, or delayed gastric evacuation.

Two pathological conditions are almost invariably accompanied by hyperacidity, namely, *duodenal ulcer* (p. 444) and *pyloric obstruction* (non-malignant). In the latter condition secretions and food materials accumulate in the stomach. The gastric contents are in consequence greatly increased, the stomach becomes dilated and large quantities of fluid are vomited from time to time. The loss of acid through vomiting may result in a condition of alkalosis accompanied by tetany (p. 701). The gastric distention occurring in this condition probably serves as a stimulus to secretion (p. 433).

The neutralization test. This test is of value in investigating the acid-regulating mechanism in duodenal ulcer especially in determining the success or otherwise of an operation performed for its cure. Instead of stimulating gastric secretion by a test meal or histamine injection, 300 cc. of 0.5 per cent hydrochloric acid solution are introduced through a rubber tube, into the fasting stomach after its contents have been removed by aspiration. Samples of the acid solution are withdrawn from time to time as in the ordinary method of fractional gastric analysis, and the total acidities determined. The results are plotted and the curve compared with a normal standard curve. In the normal subject the total acidity falls from a value of 130 at the beginning of the test to around 40 within an hour or so. In cases of duodenal ulcer the total acidity falls more slowly and may be 70 or more after the lapse of 3 or 4 hours.

CHRONIC GASTRIC AND DUODENAL ULCER (PEPTIC ULCER)

Epigastric pain coming on usually in from a half to one and a half hours after a meal and vomiting are the chief clinical features of gastric ulcer. In a certain proportion (about 20 per cent) of cases blood appears in the vomitus (hematemesis).

In duodenal ulcer, pain occurs usually within from two to three hours after a meal, that is, when

the stomach is nearly empty. The onset of the pain is therefore earlier after a light than after a heavy meal. The pain is relieved by taking food.

Pathogenesis

It is generally agreed that the dominant factor in the development of gastric and of duodenal ulcer is the action of the pepsin-hydrochloric acid of the gastric juice. The term peptic ulcer is therefore well chosen. The importance of this factor is evidenced by the following facts.

(1) Apart from the ulcerations caused by some specific disease, e.g., tuberculosis, syphilis, carcinoma, etc., ulcer of the gastro-intestinal tract is confined to those regions which are exposed to the action of acid. (a) Gastric ulcers in the great majority of cases involve the pyloric part of the stomach; they are most frequently situated on the lesser curvature near the incisura angularis or on the anterior or posterior wall in close proximity to this limited area. They are never seen in the dome of the fundus and rarely on the upper part of the greater curvature; these regions, it will be noted, are not in contact with acid for any length of time. (b) The lower part of the esophagus into which highly acid juice frequently regurgitates, and the adjacent part of the stomach wall, i.e., the cardia, are sometimes the site of ulceration. (c) Duodenal ulcer occurs practically exclusively within the first inch or less of the duodenal cap (p. 490), and nearly always upon its anterior or posterior wall, that is, where the chyme before it has been neutralized by the alkaline juices of the duodenum comes into contact with the mucosa. (d) After gastrojejunostomy, the so-called *stomal ulcer* may occur in the jejunal mucosa in the region of the anastomosis, i.e., where the gastric juice first impinges. (e) In a Meckel's diverticulum which contains ectopic gastric glands an ulcer occasionally forms. The ulcer's site is either in that part of the mucosa of the diverticulum which does not itself contain acid-secreting glands, or in the ileum at the point where the diverticulum opens into it. Matthews and Dragstedt, experimenting with dogs, produced an "artificial Meckel's diverticulum" by transplanting a pouch of the gastric wall into the ileum; an ulcer developed in the ileum just beyond the transplant in every experiment. These observations emphasize a curious fact that the commonest situations of ulcer are not in the mucosa which itself secretes the acid, but in neighboring parts which normally secrete a neutral or alkaline fluid—the pyloric region, duodenal cap, cardiac region, esophagus, jejunum

or ileum. The pyloric type of gland extends farther up the lesser than up the greater curvature (fig. 193). It has even been suggested that the occurrence of ulcers in the body of the stomach, i.e., in the acid secreting part of the mucosa, is actually dependent upon the presence of patches of aberrant pyloric glands. (f) Mann and Williamson, employing dogs, excised the duodenum and transplanted it into the ileum, thus diverting its alkaline juices away from the region of the pylorus. The cut end of the jejunum was anastomosed to the pylorus. Fourteen out of sixteen animals upon which this operation was performed developed chronic ulcers in the jejunum just beyond the pylorus. However, Fawley and Ivy found that this operation, if combined with excision of the



FIG. 193. Diagram showing the distribution of the parietal (acid-secreting) cells in the human stomach. In the black area the proportion of parietal cells was maximal and was taken as 100 per cent; in the cross-hatched area on lesser curvature the percentage of parietal cells was 75 per cent, in the shaded area at the fundus, 50 per cent, and in the white area 0 to 1 per cent. (After Berger, *Amer. J. Anat.*, 1934, 54, 87.)

fundus, or if the alkaline secretions are drained into the stomach, does not cause a jejunal ulcer.

(2) In a very large proportion of subjects of duodenal ulcer the concentration of free hydrochloric acid in the gastric contents after a test meal is abnormally high. The interdigestive or basal secretion is increased much above the normal; the pepsin concentration of the secretion is also frequently increased. According to Hurst, hyperchlorhydria (p. 443) is present in 61 per cent of cases. Of the remainder the majority show an acidity which is near the higher limit of the normal, a few have subacidity, but true achlorhydria is almost never seen. Gastric or duodenal ulcer occurs very rarely, if ever, in subjects of pernicious anemia in which gastric anacidity is almost invariable. The typical findings upon gastric analysis are: a fasting juice of greater volume than normal and of high acidity; and a

curve of gastric acidity after a test meal which rises well above (20 units or more) the normal maximum. In some cases the stomach empties more rapidly than usual as a result of exaggerated gastric motility and the curve of acidity after reaching its maximum value falls steeply again. In other instances the stomach empties in the usual time but the curve of acidity is maintained at its maximum as a result of continued gastric secretion—the *plateau type of curve*. In still other instances the emptying of the stomach is delayed as a result of pylorospasm or achalasia (see below), and the curve of gastric acidity instead of falling at the usual time continues to rise—the so-called *climbing curve* (fig. 194). High gastric acidity is less commonly associated with

with acid alone will not cause ulceration but this is readily produced by the addition of pepsin to the perfusion fluid.

(4) Measures directed toward the prevention of excessive gastric secretion and toward the neutralization of the acidity of the gastric contents are of outstanding value in encouraging the healing of the ulcer (p. 448).

Though the importance of acid in the production of ulcer cannot be denied this factor cannot be solely concerned. For one thing, many persons who show hyperchlorhydria do not develop ulcer. "Why in these instances is the gastric mucosa immune to the action of the pepsin-hydrochloric acid?" Indeed, the question has often been asked, "Why does not the pepsin-hydro-

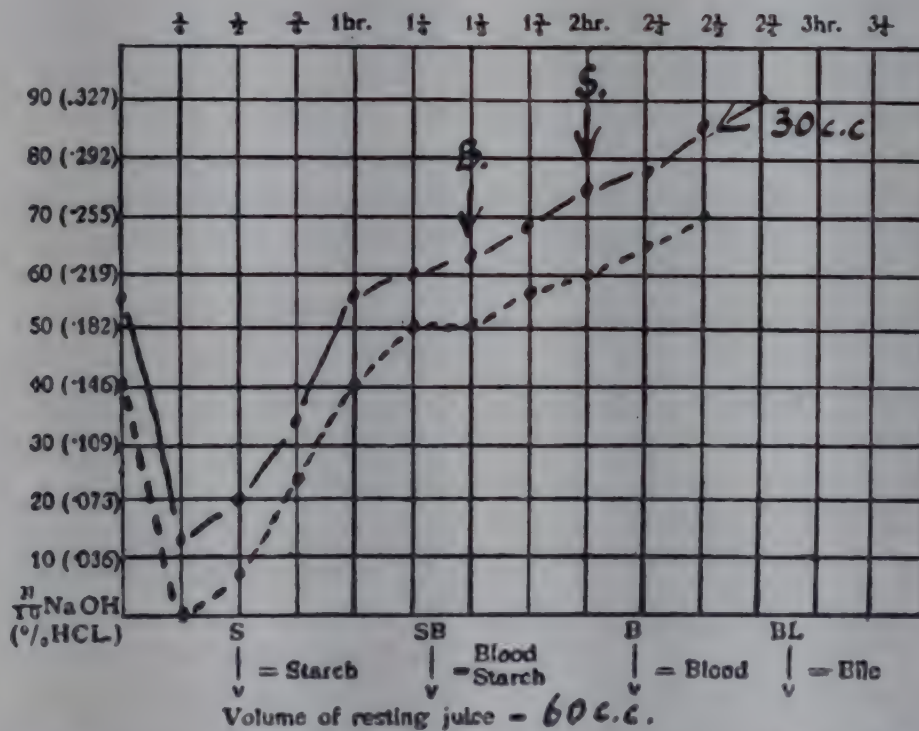


FIG. 194. Chart showing "climbing" type of curve of gastric acidity. (After Ryle.)

gastric ulcer; according to Vanzant the acidity is actually a little below the normal average. True anacidity, however, is rarely, if ever, found. The relatively low gastric acidities found in gastric ulcer are probably the result of an associated gastritis and do not necessarily indicate that hyperchlorhydria did not precede the development of the ulcer.

(3) Stimulation of gastric secretion, as by the continued administration of histamine or of caffeine (p. 447), is one of the most effective experimental means of producing gastric ulcer. Although gastric ulcers are produced experimentally by means of a constant drip over the gastric mucosa of a solution of hydrochloric acid, some pepsin must have been furnished by the stomach itself. Irrigation of a loop of jejunum

chloric acid of even normal gastric juice digest the gastric or duodenal mucosa?" It is also an extraordinary fact, firmly established by several workers, that the tissue of other parts of the intestinal tract or of other organs, though susceptible to the action of acid in their normal situations, are not digested when transplanted into the wall of the stomach. Dragstedt and Vaughn, for example, removed areas from the gastric wall of dogs and then sutured portions of the duodenum, ileum, jejunum, colon, spleen or kidney into the gaps. In no case was the transplanted tissue digested (see also p. 438). In the case of the kidney and spleen their gastric surfaces became covered with a layer of gastric epithelium. Sections of transplanted intestinal mucosa were found

to be perfectly normal after a period of nine months.

On the other hand, as shown years ago by Claude Bernard, the intact leg of a living frog is digested when introduced through a fistula into the stomach of a dog. Pavy showed the same thing for the rabbit's ear and Dragstedt and Vaughn have demonstrated that the intact limb of a live frog placed in an extract of frog's gastric mucosa is digested.

There is no satisfactory answer to the question of why the stomach does not digest its own wall. One explanation offered was that the greater alkalinity of the blood coursing through the vessels of the gastric tubules as a result of the loss of Cl ions served to neutralize the effect of the acid juice. Others have suggested that the immunity of the gastric mucosa to autodigestion is due to its containing an antipepsin. Another suggestion is that the mucin which coats the mucosa exerts a protective action.

A very interesting observation which may have a bearing upon the question has been reported by Mann and Bollman. They instilled a 0.4 per cent solution of hydrochloric acid into the stomach of dogs continuously (at the rate of 1 cc. per minute) for 8 hours daily. After a month of this treatment an ulcer formed in the region of the lesser curvature. If, however, the animal had been fed some time before the commencement of each experiment, and the remnants of food then washed away, the stomach was found to have become resistant to the action of the acid. Indeed, the acid was rapidly neutralized. Peptones appear to be responsible for the protective action displayed. The preventive action of proteins (casein, gelatin, edestin) upon ulcer development has also been demonstrated by Matzner and others.

A CONSIDERATION OF OTHER FACTORS CONCERNED IN THE PRODUCTION OF ULCER. *Bacterial infection*, and interference with the *blood supply* to the mucosa, either as a result of emboli or thrombosis have been thought by some to be responsible for ulcer production. Except perhaps in rare instances, these are no longer believed to play a rôle. *Tobacco smoking* probably through its action in stimulating gastric secretion appears, in some instances at any rate, to encourage ulcer formation or to interfere with the healing of an ulcer already formed. *Trauma*, although not essential to the production of ulcer is probably often a contributory factor. It is not difficult to believe that in the presence of other causative factors,

rubbing of food against the gastric mucosa or the passage of coarse indigestible material into the duodenal cap, will encourage the production of ulcer, or retard the healing of one already present. It is to be remembered that food after entering the stomach passes along the lesser curvature, i.e., through the *magenstrasse* (p. 484), and, as already mentioned, this region is one of the commonest sites of gastric ulcer. Experimental erosions in this situation heal much more slowly than do those produced along the greater curvature. Mann and Bollman also point out that the site of duodenal ulcer corresponds to the area of mucosa upon which the gastric contents impinge, and, when the gastric movements are energetic, this may occur with considerable force. They found that the experimental production of ulcer was considerably delayed if the propulsive force of the stomach was reduced by making an hour-glass constriction in the pre-pyloric region. Ivy and his associates have also shown that in the rabbit coarse food retards the healing of an area of the stomach wall from which the mucosa has been excised.

The neurogenic element in the production of ulcer

Cushing was the first within recent years to stress the importance of nervous influences in the pathogenesis of ulcer. He drew attention to the relatively high incidence of acute gastric ulcers after intracranial operations. Others previously had remarked upon the association of tumors of the mid-brain and diencephalon with gastric or duodenal ulcers, and the older pathologists had mentioned the frequency of softening of the gastric wall (gastromalacia) and other gastric lesions in subjects dying of cerebral conditions. Cushing suggests that the influences arising in the parasympathetic center in the hypothalamus (p. 883) and conveyed along the vagus nerves, are responsible for changes in the gastric mucosa which lead to the development of ulcer.

The experimental investigations of a number of workers support this conception. Beattie, for example, produced areas of hyperemia and small erosions in the gastric mucosa (lesser curvature) for stimulation of the hypothalamus in the region of the tuber cinereum. Keller and his associates have observed ulcerations of the stomach and proximal duodenum with small hemorrhages, following lesions of the hypothalamus. Hyperemia and erosions of the gastric mucosa have also been produced by the injection of pilocarpine (a parasympathetic stimulant) into the third ventricle or by continued stimulation of the vagus nerve.

It may also be recalled that stimulation of the hypothalamus in the region of the tuber cinereum is followed by movements of the stomach (p. 484), and that hypersecretion and gastric hypertonus (steer-horn type of stomach) are prominent features of duodenal ulcer. Moreover, it is recognized that the nervous "highly strung" type of person is more likely to be the subject of ulcer than is the phlegmatic type, and that an ulcer in the process of healing not uncommonly relapses as a result of some nervous influence, worry, emotional shock, etc. Babkin suggests the possibility that vagal impulses cause the liberation of histamine in the gastric mucosa. Through its vasodilator action and stimulating effect upon the parietal cells, conditions favorable to ulcer production are provided, namely, high gastric acidity and, through capillary stasis, defective blood supply to the mucous membrane.

The experimental production of gastric ulcer. Besides the methods already mentioned, namely, by diverting the alkaline secretion into the ileum and stimulation of the hypothalamic region, gastric ulceration can be produced in animals by the daily oral administration of *cinchophen* or by the injection of *pitressin*. Gastric ulcers can also be produced by the continued action of *histamine* or *caffeine*. They are administered intramuscularly in beeswax in order to prolong their stimulating effect upon gastric secretion. The mode of action of *cinchophen* (which also in large doses causes liver damage) is unknown. *Pitressin* (or *pituitrin*) apparently induces superficial necrosis of the mucosa as a result of vascular spasm (see Dodds and associates). Byrom has shown that following *pituitrin* administration necrotic areas accompanied by small hemorrhages occur in other organs as well.

The cause of the pain in duodenal ulcer

As already mentioned the pain of duodenal ulcer commences when the stomach is nearly empty, that is, usually about three hours after a meal. There is not general agreement as to the mechanism whereby the pain is produced. It is generally conceded, however, that it is not due to the direct stimulation of pain endings in the ulcer by acid or by food; pain fibers of the gastro-intestinal tract are not sensitive to chemical or the ordinary types of mechanical stimuli, tension is their adequate stimulus (p. 516). Nevertheless, that the acidity of the chyme is an important factor in the production of pain is evidenced by the experiments of Palmer and others. Palmer found that the introduction of 300 cc. or so of a 0.5 per cent solution of hydrochloric acid into the empty stomach of ulcer patients caused pain. This procedure

aroused no sensation in normal persons. The pain is therefore considered by most observers to be a consequence, though an indirect one, of the stimulation of afferent nerves in the base of the ulcer by the acid chyme. Disturbances of the motor mechanism of the stomach or duodenal cap (p. 484) dependent upon reflexes initiated from the irritable focus are believed to be the cause of the pain.

An observation of Dragstedt and Palmer suggests that in some instances the nerves of the ulcer, as a result of inflammation, may have become so hypersensitive that they give rise to pain in response to stimuli to which healthy visceral nerves are insensitive. It was found that gentle stroking of the surface of an ulcer, in a conscious patient during an operation, caused pain. Although spasm of the intestinal muscle occurred in the region of the ulcer, and this was painful, the ulcer surface itself appeared to be directly sensitive to mechanical and chemical stimulation. Irrigating it with acid was followed by pain which was relieved by the application of sodium bicarbonate.

Although motor disturbances of the pyloric and duodenal region are probably, in most instances, responsible for the ulcer pain, there is not general agreement as to their precise nature. According to some, spasm of the pylorus (pylorospasm), is responsible. Hurst considers that *achalasia* of the sphincter, i.e., a failure to relax upon the approach of a peristaltic wave (p. 516) rather than actual spasm exists. The immediate cause of the pain he believes to be the distention of the wall of the pyloric antrum as a powerful peristaltic wave drives fluid downwards against a pylorus which fails to open. The observations that pain may occur in the absence of peristaltic activity in the stomach, and be absent during gastric hypermotility, and that the pain is often continuous rather than intermittent, are opposed to this conception. Ryle attributes the pain to a general increase of gastric tone. The researches of Wilson indicate that the pain of duodenal ulcer is due to contraction of the duodenal cap. He examined the stomach of patients with duodenal ulcer under the fluoroscope after the ingestion of a barium meal, and during the pain. By moderate pressure upon the stomach through the abdominal wall he was able to drive fluid through the pylorus. In 14 out of 16 subjects the entrance of fluid into the duodenal cap was followed by relaxation (receptive relaxation) of the latter and the relief of pain. The ease with which material

was pressed into the cap argues against the existence of a degree of pylorospasm, or achalasia which could result in painful distention of the antrum. Furthermore, in many instances pain was experienced though the stomach was free from peristalsis. In view of these observations associating contractions of the wall of the duodenal cap with ulcer pain, it is quite conceivable that such contractions by causing tension (the adequate stimulus for gastro-intestinal pain) to be exerted upon inflamed nerve endings in the base of the ulcer are responsible for the sensation.

On the other hand, if the pain originates in this way how are we to account for the immediate relief which frequently follows the ingestion of food or of sodium bicarbonate? The relief, in some instances, occurs too rapidly to be accounted for simply by a reduction in acidity of the gastric contents. Are we to assume that in the case of bicarbonate ingestion the gas evolved passes at once through the pylorus and causes relaxation of the walls of the duodenal cap in the same manner as does fluid material forced through the pylorus by manual pressure? On the other hand, does the ingested food, or the evolved gas, by increasing the volume of the gastric contents abolish the pain by causing an adaptive relaxation of the gastric walls (p. 484). This is Ryle's suggestion. Definite answers to these questions are not forthcoming and the immediate cause of the pain of duodenal ulcer is still under debate.

Pain, in some instances, is due, apparently, to the spread of the inflammatory process to the serous coat and the traction of peritoneal adhesions. Pain of this nature is influenced by posture, disappearing usually when the subject reclines.

The application of physiological principles to treatment

The modern medical treatment of duodenal ulcer comprises the following measures. (a) Meals at frequent intervals; this practice has the two-fold effect of reducing gastric acidity and furnishing digestive products (probably peptones) which, as shown by the experiments of Mann and Bollman, exert a protective action against the action of acid. (b) The inclusion in the diet of such materials as cream and milk which, by inhibiting gastric secretion, causing the expulsion of bile from the gall-bladder and stimulating the

secretion of pancreatic juice, tend to reduce the acidity of the duodenal contents. (c) The limitation of highly seasoned foods and materials rich in extractives, especially meats and alcohol, which stimulate the gastric glands. (d) The omission from the diet of coarse indigestible articles, e.g., raw fruits and vegetables, which are likely to cause mechanical irritation of the ulcer. (e) The administration of alkalis, such as sodium bicarbonate to neutralize the acid, or of mucin which has a high acid-combining power (p. 427), and serves to form a protective coating for the ulcer. Entero-gastrone (p. 436) has recently been advocated as a means of inhibiting gastric secretion and motility. There is real danger of inducing alkalosis by the prolonged administration of readily absorbable alkaline salts such as sodium bicarbonate. Tri-calcium phosphate, calcium carbonate and magnesium oxide, and colloidal aluminum hydroxide although less efficient antacids are much less likely to induce alkalosis owing to their relatively slight absorption. The last mentioned chemical also inhibits secretion and inactivates pepsin. (f) Atropine is sometimes employed to reduce secretion. (g) The avoidance of overwork, mental or physical fatigue, worry or any psychic state likely to bring the neurogenic factor into play (p. 446).

In the treatment of duodenal ulcer, surgery is resorted to much less frequently today than in the past. When some complicating feature, (e.g., hemorrhage, perforation or pyloric obstruction) calls for operative treatment, one or other of the following procedures is usually undertaken with the object of effecting a radical cure. (a) Excision of the ulcer and reconstruction of the duodeno-pyloric region (pyloroplasty). (b) Anastomosis of the jejunum to the posterior aspect of the stomach at the lower part of the greater curvature (posterior gastroenterostomy). (c) A combination of (a) and (b). (d) Resection of the pyloric region of the stomach and of the ulcer-bearing area, and then either (i) anastomosing the cut end of the duodenum directly to the gastric stump (Billroth I type of operation), (ii) closing the duodenum and the gastric stump and performing a posterior gastrojejunostomy (Billroth II operation) or (iii) closing the duodenum and joining the jejunum to the gastric stump (Polya-Balfour operation).

CHAPTER XLI

DIGESTION IN THE INTESTINE

THE PANCREAS

STRUCTURE. (The pancreas is a racemose gland, its alveoli resembling those of the salivary gland in their general arrangement and design. Lying between the alveoli are groups of cells constituting the Islands of Langerhans which furnish the internal secretion of the pancreas (insulin, p. 577). The cells which line the alveoli and furnish the ferments of the pancreatic juice, contain, like the serous cells of the salivary glands and the chief cells of gastric tubules, zymogen granules which become reduced in number during secretory activity but re-accumulate after a period of rest. Two distinct zones may be seen in these cells, an inner lying next the alveolar lumen and containing the zymogen granules, and an outer which is clear and homogeneous. During secretion the outer clear zone increases in area at the expense of the granular zone.

The secretion is collected by a branching system of ducts which eventually lead into the main pancreatic duct—*duct of Wirsung*. This discharges in company with the common bile duct into the ampulla of Vater, which opens through a small orifice, situated upon the summit of a small papilla about $3\frac{1}{2}$ inches below the pylorus. In a certain proportion of cases the pancreatic and common bile ducts open into the intestine by separate orifices. An accessory pancreatic duct—*duct of Santorini*—is usually present. It opens into the duodenum about $\frac{3}{4}$ inch above the duct of Wirsung; it also sends a branch to the latter through which it delivered the greater part of its contents.

THE COMPOSITION OF PANCREATIC JUICE

The composition of pancreatic juice is given in table 33 modified from Starling. Its pH is between 7.10 and 8.20 (in dog).

The ferments of pancreatic juice are *trypsin*, *chymotrypsin*, *amylase*, *lipase*, *rennin* and *maltase*. Unlike the gastric enzymes, apparently those of pancreatic juice are produced by one type of cell.

Pancreatic proteinases

There are at least two proteinases in pancreatic juice—*trypsin* and *chymotrypsin*. A third, *heterotrypsin* has been described. Trypsin is not secreted as such but in an inactive form called *trypsinogen*. The activation was first shown by Schepowalnikow in Pavlov's laboratory to be brought about by the addition of a small quantity of intestinal juice or extract of the intestinal mucosa. The activation is due to an enzyme

called *enterokinase*. It has been denied by some (e.g. Waldschmidt-Leitz) that enterokinase is a true enzyme, but, as a result of the work of Kunitz, its enzymic nature is now accepted. Pure trypsinogen is also activated by allowing it to stand in a neutral solution, by the addition of trypsin, of magnesium or ammonium sulphate, or by allowing the pancreas to lie in a slightly acid solution before extraction. Calcium salts also have the power to activate trypsin. Chymotrypsin is also secreted in an inactive form, *chymotrypsinogen* and is activated by enterokinase but not by trypsin. These two enzymes, trypsin and chymotrypsin, are mainly responsible for the proteolytic activity of pancreatic juice. Both enzymes are proteins and they, as well as their precursors, have been obtained in pure crystalline form. Trypsin has no milk-curdling power, but is capable of clotting blood, whereas chymotrypsin, although it will not cause coagulation of blood has a powerful milk-curdling action, and is probably identical with pancreatic rennin. The optimum pH for the action of trypsin and of chymotrypsin is around 8; that of enterokinase is within the range between pH 5.2 to pH 6.0.

The *action* of trypsin carries the digestion of protein beyond the peptone stage. It also differs from peptic digestion in being carried on in an alkaline instead of in an acid medium. It is possible, moreover, that different linkages in the protein molecule are attacked by the two enzymes. Though under ordinary circumstances trypsin is called upon to commence its action after the gastric juice has converted a large part of the protein into proteoses and peptones, it can also attack native protein; flesh introduced directly into the duodenum is readily digested by the pancreatic juice. Nevertheless, the preparatory digestion of protein by gastric juice is favorable to tryptic action. The specific action of trypsin is to break the proteose and peptone fragments of the protein molecule into smaller amino-acid groups. These are generally termed *peptids*. In the earlier stages of tryptic digestion the amino groups are for the most part still relatively large—*poly-peptids*. Some of these are later split into groups containing 2, 3 or 4 amino-acids, constituting the *di-peptids*, *tri-peptids* and *tetra-peptids*; even a few

individual amino-acids, such as tyrosine and tryptophane are released. The complete breakdown of protein is reserved for the erepsin of the succus entericus (p. 455). The pancreatic juice itself also contains a small amount of erepsin.

Pancreatic amylase (amylopsin or diastase)

This has an action similar to but much more powerful than that of salivary amylase (ptyalin, see p. 421). In the hydrolysis of starch by pancreatic juice the same stages are passed through as have already been described for salivary digestion but they are completed in a fraction of the time, most of the starch being converted into maltose within a few minutes. Due to traces of *maltase* small amounts of glucose are also formed in the final stages of the pancreatic digestion of starch. Pancreatic amylase unlike the corresponding salivary enzyme is capable of digesting unboiled

TABLE 33
(Modified from Starling)

	SECRETIN JUICE FROM THREE DOGS (SP. GR. 1014)	PILOCARPINE JUICE
Alkalinity; Number of cc. of N/10 NaOH equal to 10 cc. juice.....	12.7	5.5
Total solids in 100 cc.....	1.58 gm.	6.4
Total proteins in 100 cc.....	0.5	4.8
Ash in 100 cc.....	0.96	1.3
Chlorides in 100 cc.....	0.30	0.27
Total nitrogen.....	—	0.74

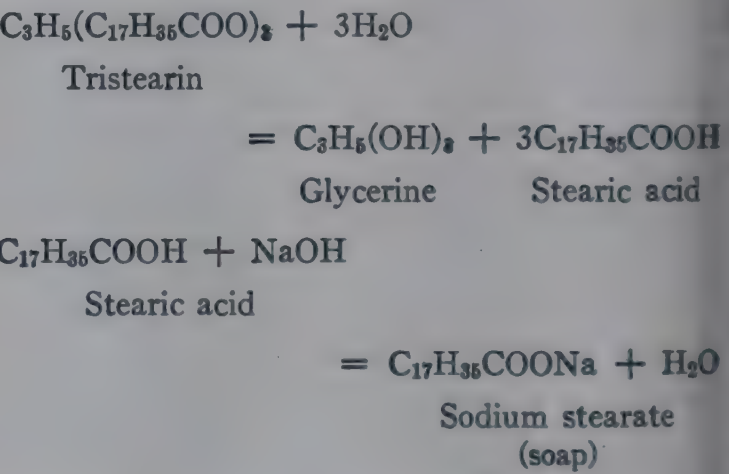
starch. Raw corn and wheat starch may be converted entirely into maltose, and raw potato starch is transformed to the extent of 80 per cent. It is important to remember in connection with infant feeding that during the first few weeks of life pancreatic amylase, the only really efficient ferment for the digestion of starches, is absent from the pancreatic juice. Little provision has been made for the digestion at this time of any other food than the natural one—milk.

The amylolytic ferment of the pancreas acts in a neutral, slightly alkaline or slightly acid medium. It acts to best advantage when the medium is faintly acid or neutral in reaction, its pH optimum ranging from 6.7 to 7.0. Certain inorganic ions, especially Cl, are absolutely essential for its action; if these be separated from pancreatic juice by dialysis the juice is deprived of its starch-splitting power. Part of the diastase is believed

to be re-absorbed from the intestine and excreted in the urine (p. 451).

Pancreatic lipase or steapsin

Fat is not digested to any important extent until it has reached the intestine. Here the lipase splits the fat molecule into its constituents, fatty acid and glycerine (see p. 593). A certain proportion of the fatty acids combine with the alkali in the intestinal fluids to form soaps. These through their property of lowering surface tension aid the division of the fat into smaller globules; a finer emulsion of fat with the intestinal juices results and the total surface area of the fat exposed to enzyme action is thereby increased.¹ The bile salts (p. 457) have a similar but more important effect upon the emulsification process. They therefore greatly enhance the fat-splitting action of steapsin. The reactions are shown in the following equations.



Pancreatic rennin has an action similar to that of gastric rennin (p. 427), but the pancreatic juice has a much more powerful milk-curdling power than has gastric juice. It is probable that the action is not due to a separate enzyme but to chymotrypsin (p. 449).

Disorders of the digestive function of the pancreas

In chronic pancreatic disease (chronic pancreatitis) the digestive power of the juice secreted by the gland becomes markedly reduced with the result that the feces contain quantities of undigested fat, protein and starch. The stools are increased in bulk and pale, and there may be diarrhea (pancreatogenous diarrhea). Several clinical tests have been devised in order to determine the extent of the impairment of the digestive functions of the gland. The microscopical examination of the feces for intact muscle fibers after a meal of

¹ Soaps are not formed in an acid medium; any which have been formed in the alkaline juices become precipitated again as the acidity of the intestinal contents increases.

meat, or the estimation of the fecal fat often gives valuable information. Others estimate the enzyme activity of the duodenal contents withdrawn through a duodenal tube. *Acute pancreatitis* is associated with severe abdominal pain, vomiting and symptoms of shock. In the more severe types of the acute disease hemorrhages into the glandular substances with necrosis occur. Fat necrosis in the mesentery, omentum and peritoneum, as well as in the pancreas itself is commonly observed. This is caused by the escape of lipase from the disorganized gland.

Hemorrhagic pancreatitis has been thought to be the result of the obstruction of the outlet of the ampulla of Vater (gallstone, spasm of sphincter of Oddi or swelling of duodenal mucosa) and the passage, in consequence, of bile into the pancreatic duct system (Archibald). However, according to Dragstedt and his associates only about 60 per cent of cases of hemorrhagic pancreatitis arise in subjects of chronic biliary tract disease and in only about 10 per cent of these is the ampulla obstructed by a gallstone. Rich and Duff find that the reflux of bile into the pancreatic ducts is a rather infrequent accompaniment of hemorrhagic pancreatitis. When reflux of bile is observed obstruction of the pancreatic duct system with subsequent rupture of the duct wall and the escape of pancreatic juice into the interstitial tissue of the pancreas is believed by these observers to be the essential factor in the production of the hemorrhagic lesion, rather than the action of the bile itself. Obstruction to the flow of pancreatic juice, due to metaplasia of the epithelial lining of a branch of the pancreatic duct within the gland, is considered by Rich and Duff to be the commonest cause of acute pancreatitis. The ductules and acini behind the obstruction become dilated; rupture of the distended walls and the escape of digestive enzymes into the glandular substance is looked upon as the immediate cause of the disease. The interstitial tissue of the pancreas, in common with other tissues of the body, possesses the power to activate the trypsinogen of the pancreatic juice; digestion and necrosis of the blood vessels result. These observers found metaplasia of the duct epithelium and acinar dilatation in 13 of 24 cases of hemorrhagic pancreatitis. In most cases of the disease a gallstone was not found in the ampulla of Vater and the main pancreatic duct was unobstructed. It is pointed out that rupture of a dilated ductule or acinus is most likely to occur when the secretion pressure of pancreatic juice is high, i.e., after a large meal or the ingestion of alcohol.

A determination of the concentration of the amylase or lipase of the serum or of the output of amylase in the urine is valuable as a means of recognizing acute pancreatic disease. In pancreatic damage the urinary amylase and the concentration of amylase in the serum are greatly increased. A corresponding rise occurs in the serum lipase. The *secretin test* is of great value in investigation of pancreatic insufficiency, especially in chronic disease e.g. cystic fibrosis of the pancreas. In

performing the test a purified preparation of secretin is injected intravenously and the duodenal secretions withdrawn by suction through a duodenal tube. The secretions are collected in 20 minute periods for an hour following the injection and the enzyme activity (trypsin, lipase, amylase, and phosphatase) determined.

THE EFFECTS OF THE TOTAL DRAINAGE OF PANCREATIC JUICE TO THE EXTERIOR. Elman and McCaughan have demonstrated the fatal effect of the loss from the body of all the pancreatic juice. In dogs the survival time following the establishment of a pancreatic fistula through which the juice was drained to the exterior was from seven to eight days. Loss of electrolytes with consequent dehydration (p. 18) is undoubtedly a factor leading to this result, for the life of the animals can be prolonged by the intravenous administration of Ringer's solution. Death cannot, however, be prevented by this treatment, the animals succumbing in spite of it after some weeks. Nor do the animals die simply as a result of inanition, for it has been shown that in the absence from the intestine of the pancreatic juice as a result either of a pancreatic fistula or of pancreatectomy, sufficient quantities of food are digested and absorbed to maintain life for indefinite periods. It has been suggested, therefore, that the loss of some material essential to life other than salts and water is the cause of death.

Ligation of the pancreatic ducts in dogs is followed by defective digestion of all three types of food stuff. There is pronounced polyphagia, loss in weight and impairment of liver function (Ivy). The general nutrition of the animals is improved by feeding raw pancreas. No compensatory increase in the secretion of the enzymes of the succus entericus occurs.

THE REGULATION OF THE SECRETION OF PANCREATIC JUICE

The secretion of pancreatic juice is under both hormonal and nervous control.

The hormonal control

In 1902 Bayliss and Starling showed that an acid (HCl) extract of the duodenal mucosa when injected into the blood stream of an animal caused a copious flow of pancreatic juice. Intravenous injection of the acid itself was ineffective. A secretagogue effect also followed the introduction of acid into a loop of bowel whose nervous connections had been completely severed, the only communication between the bowel and the pancreas being then through the blood stream. The secretory effect was shown to be specific and not simply due to vasodilatation of the pancreatic vessels. The excitatory substance was called *secretin*.

The obvious physiological implication of these results was that the acid chyme upon coming into

contact with the duodenal mucosa caused the production, or liberation, of a substance which was then conveyed by the blood to the pancreatic cells. Ivy, Farrell and Lueth transplanted a loop of intestine and the tail of the pancreas to subcutaneous sites, thus isolating the two structures completely from extrinsic nervous control. They observed secretion from the pancreatic transplant when acid was placed in the isolated loop. Since the intravenous injection of acid alone is ineffective, this experiment affords conclusive evidence for the liberation of a hormone from the intestinal mucosa.² Mellanby and Huggett in 1926 demonstrated that secretin existed preformed in the mucosa from which it could be extracted by water, alcohol and other solvents as well as by acid. Bayliss and Starling had claimed that the hormone existed in an inactive or precursory form which they called *prosecretin*. Mellanby also showed that bile introduced into the duodenum caused secretin to be absorbed into the blood stream and that the active agent in the bile was the cholic acid of the bile salts. He suggested that the bile salts in their passage through the intestinal mucosa absorbed the secretin and carried it into the blood. Bile salts, however, though aiding in the absorption of the hormone are not absolutely essential. Ivy and his colleagues have shown that food (meat and fat) entering the intestine stimulates pancreatic secretion in the usual manner after ligation of the common bile duct.

The action of secretin is not reduced by atropine which paralyzes vagal endings or by ergotamine which paralyzes sympathetic secretory fibers; so there is no evidence that its production or absorption is influenced by nervous mechanisms, or that it stimulates parasympathetic or sympathetic terminals in the pancreas. It appears to be a direct excitant of the glandular cells. Secretin also stimulates the secretion of bile and probably of the succus entericus. Its chologogue effect is a direct one and not simply secondary to the liberation of metabolites from the activated pancreas.

Agren and associates have prepared secretin in pure crystalline form. It is a protein-like substance (molecular wt. 5000) giving a positive biuret but a negative ninhydrin reaction. It is basic in character, containing histidine and arginine but is free from cystine, tyrosine and tryptophane. This preparation and a cruder but non-toxic amorphous material have been used by these workers to test biliary and pan-

creatic functions in man. Ivy and Greengard have obtained secretin in the form of a crystalline picrolonate with the formula C_8H_5ON . The highest yield of secretin is given by the upper two-thirds of the small intestine. Minimal amounts are obtained from the lower third of the small intestine and from the ascending colon. It is absent from the gastric mucosa.

Pancreozymin. This is the name which Harper and Raper have given to a second pancreatic hormone obtained, like secretin, from extracts of duodenal mucosa. The existence of this hormone has been confirmed by Greengard and his associates. Unlike secretin it stimulates the secretion of trypsin, amylase and lipase.

The control of pancreatic secretion by nerves

It has been known since the important work of Pavlov on pancreatic secretion that the gland cells are excited by vagal impulses. Control of pancreatic secretion by the vagus was shown in the following way. The nerve was divided in the neck four days previously. This preliminary procedure has the effect of practically abolishing the irritability of the cardiac fibers since they degenerate before the secretory fibers. When the nerve prepared in this way is stimulated a well-marked secretion of juice occurs. The secretion is, however, much less pronounced than that which follows the injection of secretin. On this account it had been assumed that the secretion following nerve stimulation was of little importance. Mellanby has shown that this view is erroneous. The vagal secretion, though thick and scanty, is particularly rich in ferments. Indeed the secretion of ferments is mainly under vagal control. The chief effect of secretin, on the other hand, is to cause the secretion of the water and inorganic constituents, e.g., the bicarbonate of the pancreatic juice. Vagal stimulation causes exhaustion of the zymogen granules. Only after repeated injections of secretin do histological changes of a similar nature appear, and these are always less pronounced than those following nerve excitation. Apparently then, the extrusion of the colloidal zymogenous particles from the cells into the alveoli is largely controlled by nervous impulses. The hormone, on the other hand, causes a flow of alkaline fluid which serves to flush the alveoli, to thin the juice rich in organic materials and sweep it along the ducts. Pilocarpine acts similarly to vagal stimulation. Atropine annuls the nervous secretion but, as already mentioned, not that caused by secretin. Under certain circumstances a small secretion of pancreatic juice may be obtained by stimulation of the splanchnic nerve.

² The word, hormone, was used for the first time as a result of these experiments. They also furnished the first conclusive evidence of a hormonal mechanism.

This is probably a vascular effect. Pavlov showed that there is a psychic element in the control of pancreatic secretion. Though the effect is much less than in the case of gastric secretion, sham feeding was found very definitely to increase the pancreatic flow—a result which Ivy has confirmed.

THE ACTION OF THE CHYME UPON PANCREATIC SECRETION

Chyme escaping through the pylorus causes an approximately equivalent amount of alkaline fluid (bile and pancreatic juice) to enter the intestine. Among the substances in the chyme which exert the greatest secretagogue effect upon the pancreas are acids, meat extracts, protein derivatives, fats, fatty acids, soaps and water.

There is evidence that peptones, acids and soaps exert their action through local reflex mechanisms and that these in turn are influenced by vagal impulses. Crider and Thomas found that the effect of peptones and of acid (but not of soap) upon secretion was abolished immediately after section of the vagus nerves. Recovery occurred a few days later but the juice was reduced in volume and in its concentration of total nitrogen. They suggest that the vagus exerts its control upon the pancreatic secretion not directly but through augmentation or inhibition of the activity of the local reflexes.³ The splanchnic nerves, on the contrary, appear to be without effect upon pancreatic secretion initiated by chemical stimulation of the intestine. Peptone stimulation causes the secretion of a juice resembling that resulting from vagal stimulation, being of higher specific gravity and with a nitrogen concentration many times greater than that caused by acid, water or secretin. Peptone stimulation is also accompanied by depletion of the zymogen granules of the acinar cells (Ramsay, Thomas and Crider). It is possible that certain other products of digestion may enter the circulation and be carried directly to the gland (humoral mechanism, p. 434).

The adaptation of the concentrations of amylase and trypsin in the pancreatic juice and tissue to the predominant element of the diet

Grossman, Greengard and Ivy found that the amylase concentration in the pancreatic juice and tissue of rats maintained upon a diet predominantly carbohydrate was greatly increased and the trypsin content decreased. In animals on a high-protein diet,

³ It may be, as Greengard and his associates suggest, that the vagus exerts its effect simply through causing vasodilatation.

the trypsin content of the pancreas was increased and the amylase content reduced. A high fat diet had little effect, however, upon the production of pancreatic lipase or of trypsin but reduced the concentration of amylase in the pancreatic juice and tissue. The hydrolytic product of starch, namely, dextrose, increases the amylase content of the pancreas, but the products of protein(casein) have no such action upon trypsin production. Grossman and his associates suggest that amylase production is regulated through a humoral mechanism involving dextrose, whereas the tryptic content of the pancreas is controlled reflexly.

THE INTESTINAL JUICE

THE STRUCTURE OF THE INTESTINAL GLANDS

The intestinal juice or *succus entericus* is the name given to a specific secretion of innumerable glands scattered diffusely over the mucosa of the small intestine. The glands consist of minute tubular pits—the *crypts of Lieberkühn*—lined by cells which are continuous with the general epithelial covering of the mucosa. Glands of a similar character are present in the large intestine, including the appendix but their secretion possesses little or no digestive action. Confined to the duodenum, and especially numerous in its upper part, another type of gland is found; this is the gland of Brunner. The glands of Brunner resemble the gastric glands of the pyloric region and, like the latter, are tortuous and branching. Their secretion, also, like that of the pyloric glands, is alkaline; it contains mucus and a weak proteolytic ferment.

To the naked eye the mucosa of the small intestine presents a velvety appearance, due to the presence of immense numbers of minute slender processes which—like the pile of velvet—project from its surface. These are the *intestinal villi*. They are barely visible individually to the unaided sight and number from 20 to 40 to the square millimeter. They are absent from the large intestine. Each villus shows a lymph vessel (lacteal) which occupies its axis from the base to near its tip. An arteriole enters each villus, and from this a capillary plexus arises from which the blood is returned by one or two larger venules. The deeper regions of the pits formed between adjacent villi dip into the submucosa and constitute the intestinal glands or crypts of Lieberkühn (fig. 195). The cells covering the somewhat club-shaped extremities of the villi are columnar in shape, and peculiar in that their free borders show a very fine striation, the striae running perpendicular to the free surface of the cell. Many of the columnar cells become transformed into goblet cells and secrete mucus.

The cells lining the crypts of Lieberkühn are of four

types. (a) *Columnar cells*. (b) *Goblet cells*. These two types of cells are similar to those of the villi but do not possess the fine striations just referred to. The more superficial portion of the gland tubule is lined by these two cell types alone. (c) Large flask-shaped cells which stain with silver ammonium oxide. They are therefore known as *argentaffin cells* or *cells of Kultschitzsky*. These cells contain granules but their function is a disputed question. According to some they are endocrine elements, while others believe they supply ferments to the intestinal juice. (d) *Cells of Paneth*. These lie in the blind extremity of the glands of the ileum but not in those of the duodenum. Their

establishment of a *Thiry fistula*. This consists in completely isolating a loop of small bowel from the rest of the intestinal tract by two incisions placed from 6 to 10 inches apart, and then restoring the continuity of the bowel by an end to end anastomosis of the sections above and below the isolated portion. The blood vessels and nerves reaching the loop through its mesentery are left intact. One end of the loop may be closed by suture, the other end being left open and brought through the abdominal wound where it is fastened by sutures and the abdomen closed around it.

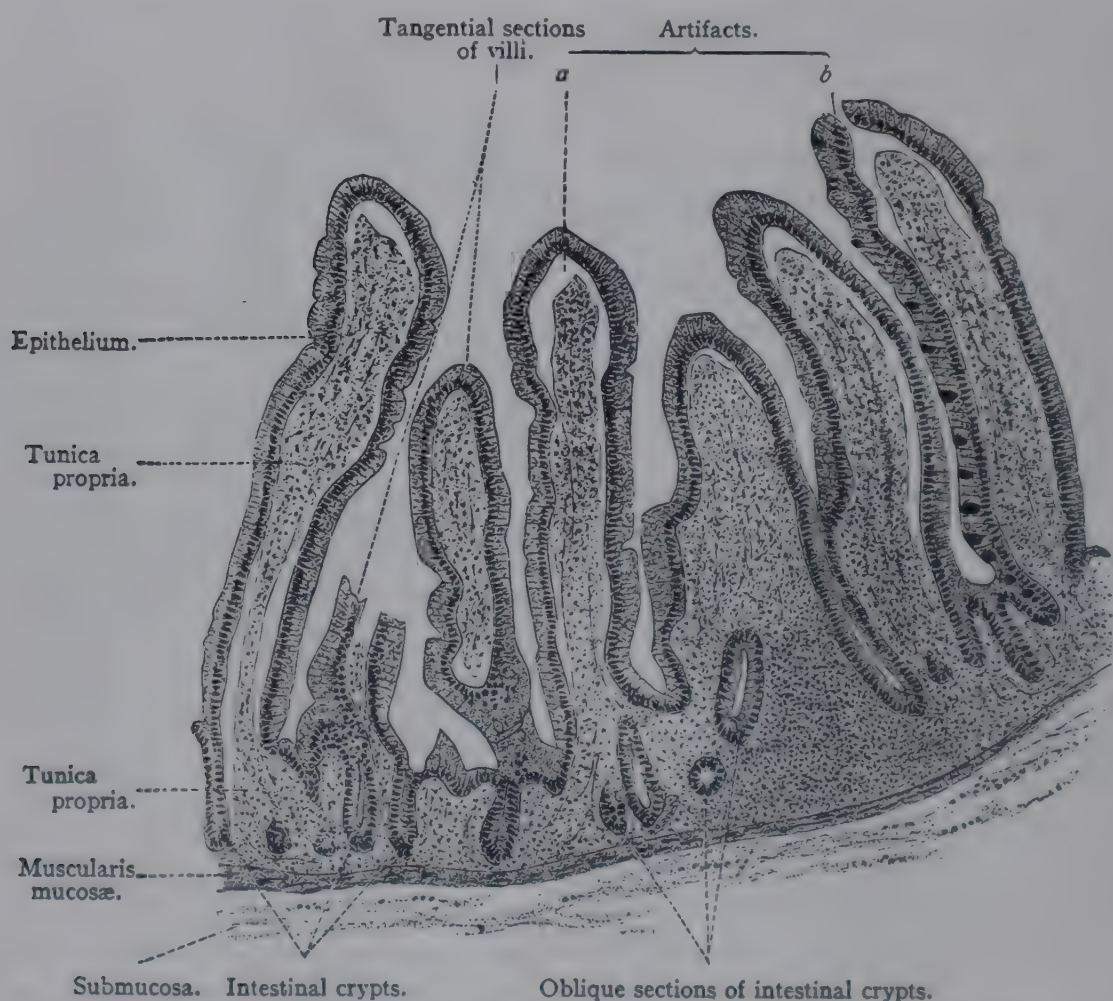


FIG. 195. Vertical section of the mucous membrane of the jejunum of adult man. The empty space, *a*, between the tunica propria and the epithelium of the villus is an artifact, the result of the shrinking action of the fixing fluid. The goblet cells have been drawn on one side of the villus on the right. (After Stöhr.)

protoplasm shows a fine reticulum and is studded with coarse granules. The function of these cells has not been definitely determined, but from their resemblance to the secretory cells of other digestive glands they are presumed to supply the ferments of the intestinal juice (fig. 196).

THE COMPOSITION OF THE INTESTINAL JUICE

Owing to the admixture of the succus entericus with the other intestinal secretions—pancreatic juice and bile—and to the fact that the glands are diffusely scattered throughout the mucosa, special means must be devised for its collection in the pure state. Pure juice may be obtained by the es-

It may be desirable to leave both ends open and stitch each into the abdominal wall a short distance apart. This constitutes a *Vella* (or *Thiry Vella*) fistula.

The *Mann-Bollman fistula*, so called after its inventors, is useful for certain types of investigation. A loop of ileum is isolated. The distal (aboral) end is anastomosed to the duodenum or any desired part of the small intestine; the proximal (oral) end is sutured to the abdominal wall. By giving the loop this direction in relation to the exterior, the peristaltic waves, which are inherently incapable of passing in any other than an aboral

direction along the bowel (p. 496) whatever the latter's position, prevent leakage from the external opening.

In man, samples of intestinal contents can be obtained by means of the Millar-Abbot tube.

The composition of intestinal juice varies greatly under different conditions. At times it consists chiefly of water and salts and has a low digestive power. At other times it is slimy from

Peptidases, erepsin

The peptids that have resisted pancreatic digestion are finally broken up into the separate amino-acids by peptidases in the intestinal juice. The juice contains several peptid-splitting enzymes, each with a specific action upon a particular type of peptid. The *succus entericus* is almost powerless to attack native protein or peptone, the protein must first have been partially digested by trypsin and have reached the peptid stage. The peptid-splitting action of the intestinal juice has until recent years been attributed to a single enzyme to which the name *erepsin* was applied by Cohnheim. The intestinal mucosa itself is rich in peptidases;⁴ their presence here would appear to afford a safeguard against the entrance of incompletely split products of protein digestion into the blood stream. Peptidases are also found widely distributed, though to variable extent, throughout the tissues of the body, as well as in various plants, yeast and even in bacteria. They are also present in low concentration in pancreatic juice. The optimum pH for the reaction of the peptidases of the *succus entericus* is around 8.0.

The intestinal wall also contains such enzymes as *nucleases*, *nucleotidases* and *nucleosidases* (p. 565). The first of these hydrolyse nucleic acids into their constituent nucleotides; the nucleotidases split the nucleotides into nucleosides and phosphoric acid; the nucleosidases separate the nucleosides into sugar (pentose) and purine bases. *Arginase*, a ferment which splits arginine into ornithine and urea (p. 546) is also present in the intestinal mucosa as well as in the liver and other tissues. *Phosphatase* (p. 716) is found in relatively high concentration in the mucosa of the small intestine.

Ferments which act upon sugars

If we except the small amounts of maltase contained in saliva and pancreatic juice, and the comparatively slight change that the HCl of the gastric juice exerts upon cane sugar, then the responsibility for the digestion of the disaccharides devolves entirely upon ferments in the *succus entericus*. *Maltase*, *sucrase* (also called *invertase*)

⁴ Though it is generally stated that these and the other enzymes in fistula juice are *secreted* it must be admitted that the experimental conditions under which the juice is collected do not exclude the possibility that its activity is due to enzymes liberated from disintegrated cells of the intestinal mucosa. Some indeed hold the view that under physiological conditions only enterokinase and amylase are actually secreted in the *succus entericus*.

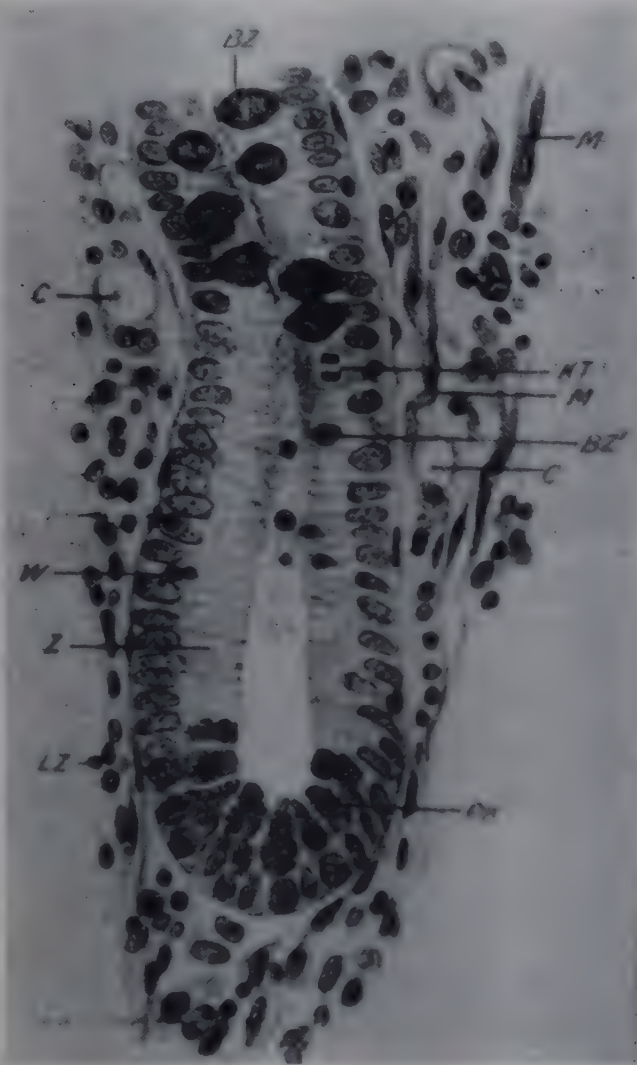
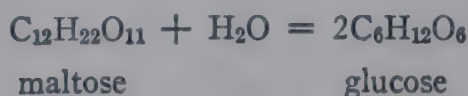


FIG. 196. A crypt of Lieberkühn with surrounding lamina propria: BZ, goblet cells; BZ', goblet cells at the end or beginning of secretion; C, capillary; KT, mitosis in an epithelial cell; LZ, lymphocyte; M, smooth muscle cells; PK, Paneth cells; W, wandering cells in the epithelium; Z, epithelial cells of the gland. (From Maximow and Bloom, after Schaffer.)

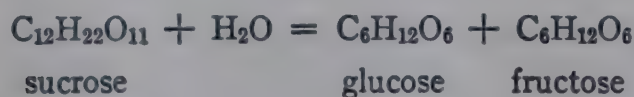
the presence of a large proportion of mucus. Its concentration in ferments varies considerably. It owes its alkaline reaction (pH from 7.0 to 8.5) to the presence of *sodium carbonate* and *bicarbonate*. It contains *enterokinase*, the activator of trypsin (p. 449).

The chief ferments of intestinal juice are;— (1) *Various peptidases (erepsin)*; (2) A ferment for each of the disaccharids, *sucrose* (cane sugar), *maltose* (malt sugar) and *lactose* (milk sugar); (3) *Lipase*; (4) *Amylase* in traces.

and *lactase* are powerful enzymes which act specifically upon the corresponding substrates to convert them into monosaccharides. A molecule of maltose is converted by maltase into two molecules of the hexose, glucose, by a process of hydrolysis according to the equation—



Similarly sucrose is split into a molecule each of glucose and fructose by *sucrase*.



Lactase converts lactose (milk-sugar) into the hexoses glucose and galactose. The enzymes acting upon the disaccharides are also present in the tissue of the intestinal wall.

Lipase

The intestinal juice contains small but not unimportant quantities of lipase; relatively large amounts of fats are digested in the absence of the pancreas or after ligation of its ducts. Fifty per cent or more of the ingested fat may undergo hydrolysis under these circumstances.

The various digestive ferments are secreted in much smaller amounts in the lower reaches of the small intestine, and in the large bowel the secretions are composed mainly of water, mucus and inorganic salts; ferments are almost entirely lacking.

THE SECRETION OF INTESTINAL JUICE

The intestinal juice is secreted continuously though in variable quantities from time to time. The activity of the intestinal glands is under *nervous and hormonal* influences.

Nervous influences. Mechanical stimulation

The glands respond very promptly and energetically to mechanical stimulation of the intestinal mucosa. The secretion then is brought about reflexly through the nerve plexuses within the bowel wall. Juice drains continuously from a loop of bowel opening to the exterior and division of the extrinsic nerves does not reduce the secretion resulting from mechanical stimulation (e.g., distention). The secretion indeed is more likely to be increased by sympathetic denervation of the loop, an observation which suggests the removal of an inhibitory influence. An experiment performed by Moreau has also led to the belief that

the sympathetic nerves exert an inhibitory effect upon secretion. This observer obstructed the bowel at three points by means of ligatures, thus forming three closed loops. The central loop was denervated. The intestine was replaced within the abdomen and the latter closed. Upon examining the loops in from four to sixteen hours later, the central loop was found distended with intestinal juice while those on either side were comparatively empty. It is possible, however, to explain this result upon a vascular basis—namely, the loss of vasomotor tone and consequent hyperemia of the denervated loop—without assuming that an inhibitory influence upon secretion had been removed.

Experimental stimulation of the vagus nerve has on the whole given inconclusive results; Wright and his associates have reported that vagal stimulation causes secretion from the upper part of the duodenum but from no other part of the intestine if the sympathetics were intact. After section of the sympathetics in the thorax a secretion from the intestine followed stimulation of the vagus.

As a result of the sensitivity of the mucosa to mechanical stimuli, undigested food residues or other unabsorbable solid material will in their passage through the bowel cause excitation of the glands and so increase the fluidity of the intestinal contents. The advantage of this in aiding the movement of food along the alimentary canal is obvious.

Hormonal influences

It is probable, though it has not been definitely proved, that secretin serves as a stimulant for the secretion of intestinal juice as well as for pancreatic secretion; according to Florey and Harding it excites the glands of Brunner. Injection of secretin into the blood stream has been reported to cause secretion from a Thiry fistula; the secretory effect is unaltered by denervation of the loop of bowel. Secretion into an isolated loop has also been observed when acid was placed in a second loop. The secretion was due presumably to the passage of secretin into the general blood stream. Pancreatic juice acting locally within the bowel lumen, according to Pavlov, also excites the intestinal glands. The juice which results is rich in enterokinase. Pancreatic juice injected into the blood stream has no such effect. Nasset and associates have isolated a substance from the mucosa of the small intestine which they believe is a specific hormone controlling the secretions of the intestinal glands. This substance, which

they have named *enterocrinin*, is free from vasodilator effects and does not stimulate pancreatic secretion. It is prepared from extracts of the small and large intestine; it increases both the volume and enzyme concentration of the succus entericus.

Secretion of mucus

Mucus is secreted by the epithelial cells (goblet cells) of the small intestine and colon. Florey in experiments upon cats concluded that the secretion of mucus by the colon was not under nervous control. Prolonged stimulation of parasympathetic fibers (pelvic nerve) or of the sympathetic was without effect. Pilocarpine, a parasympathetic drug, is also ineffective unless administered in relatively enormous doses. Mechanical stimulation of the mucosa or the application of chemical irritants, e.g., silver nitrate, mustard, iodine, or high temperature, causes a pronounced secretion of mucus. The secretion is brought about, it is believed, by direct stimulation of the goblet cells which increase in number progressively from the upper to the lower regions of the intestinal tract. The injection of histamine, acetylcholine, adenosine or peptone solutions which cause vasodilatation did not cause secretion. The chief functions of the mucus secreted by the colon are to protect the mucosa from injurious agents and, under certain circumstances, by lubricating the intestinal lining, to aid the movement of feces.

A great increase in the production of mucus by the colon is an outstanding feature of the condition known as *mucous colitis*. Abdominal pain, spastic constipation intermitting with attacks of diarrhea and the passage of masses of mucus characterize the disease. Its cause is obscure.

THE BILE

In most animals and in man, bile is secreted continuously by the liver cells. It passes along the bile capillaries, hepatic and cystic ducts to be stored in the gall-bladder. Its expulsion from the latter and its passage along the common duct into the duodenum is intermittent, related in time to the arrival of food in the intestine, and is quite independent of the actual secretion by the liver (see p. 473).

THE COMPOSITION OF THE BILE

The bile is a highly complex fluid. The physiological significance of many of its constituents is unknown; some are present only in minute amounts and are most probably merely waste products undergoing elimination. Table 34 gives the com-

position of human liver bile (parts in 1000), as analyzed by Hammarsten. Liver bile has a pH of between 8.0 and 8.6. The reaction of human gall-bladder bile is neutral or slightly alkaline; that of the dog (or cat) is definitely acid—pH between 5.0 and 6.0. The chief biliary components are the *bile salts*, *bile pigments*, *cholesterol* and *lecithin*. These organic materials make up over 60 per cent of the total biliary solids. As a result of the absorption of water and inorganic salts (p. 471) gall-bladder bile is several times more concentrated in organic solids than liver bile. The biliary constituents may vary independently of one another.

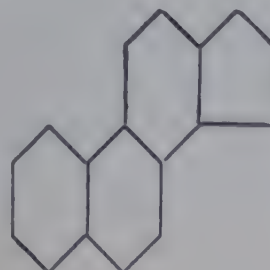
The bile salts

The bile salts are the *glycocholate* and *taurocholate of sodium*. The bile acids glycocholic ($C_{26}H_{47}NO_6$) and taurocholic ($C_{26}H_{45}NSO_7$) with which the base is combined, are formed by the

TABLE 34

Water.....	974.80
Solids.....	25.20
Mucin and pigments.....	5.30
Bile salts.....	9.30
Fatty acids from soaps.....	1.23
Cholesterol.....	0.63
Lecithin }	0.22
Fat }	
Inorganic salts.....	8.32

junction of *glycocoll* (glycine) and *taurin* ($C_2H_7NSO_3$), respectively, with *cholic acid* ($C_{24}H_{45}O_6$). The glycocholic and taurocholic acids are present in about equal amounts in the bile of the herbivora and of man. Taurocholic is the sole acid in the bile of the dog and other carnivora. Taurin is related to cysteine, a sulphur-containing amino-acid; glycine we are familiar with as the simplest amino-acid and one which can be synthesized by the body (p. 545). Glycocholic and taurocholic acids therefore contain nitrogen, but sulphur is present in the latter only. The structural formula of cholic acid contains the tetracyclic carbon group characteristic of the sterols; this is shown below in skeleton form:



Cholic acid is therefore related to cholesterol, to the male and female sex hormones (Chapter lxii) and to corticosterone (p. 692). There is no evidence, however, that in the body cholic acid is derived from cholesterol; feeding the latter causes no increase in the production of bile salts. The physiological relationship between cholic acid and the sex hormones is obscure. The precursors of cholic acid in the body are also unknown.

Nor can much be said concerning the *site of origin* of the cholic acid; whether it is formed by the hepatic epithelium, or is merely brought preformed to the liver from other body tissues is not known. That some is formed in the body is indicated by the fact that the bile salts continue to be discharged from a biliary fistula during long periods of starvation. That it is derived also from the food appears from the observation that increased excretion follows the ingestion of protein material. Though the supplies of glycocol and taurine within the body are apparently plentiful the supply of cholic acid is limited, for experiments in which taurine was fed alone caused no increase in the excretion of bile salts whereas cholic acid ingestion alone caused a rise in the excretion of taurocholic acid. It is possible to deplete the taurine stores by feeding cholic acid for several days to a dog with a biliary fistula. When cystine disulphoxide, cysteine, cysteine sulphinic acid or cysteic acid is then fed with cholic acid, an increase in the taurocholic acid of the bile follows (Virtue and Doster-Virtue). This result suggests that from such or similar compounds, taurine is produced in the body. That is, taurine under these circumstances is evidently supplied from body sources whereas cholic acid must be furnished in the diet. The quantity of cholic acid available apparently determines the level of bile acid excretion (Whipple).

So far as is known the liver is the only situation where the *conjugation* of taurine or of glycocol with cholic acid, and the production of the respective bile acid can take place. The following observations suggest that their formation is a specific function of the liver. (1) When the function of the liver is depressed by injury, or by the establishment of an Eck fistula (p. 287), the output of bile salts may be reduced by 50 per cent or more (Smyth and Whipple). (2) When the common bile duct is ligated in dogs bile acids appear in the blood. On the other hand, no accumulation occurs in the blood after removal of the liver. The liver is also the site for the destruction of bile salts, for when fed they can be recovered quantitatively from the urine of hepatectomized but not of normal animals.

THE CIRCULATION OF THE BILE SALTS. After their passage into the intestine, the bile salts undergo re-absorption and are carried in the portal blood stream back to the liver for re-excretion. This portal-biliary circulation of the bile salts is

intimately connected with the absorption of fat (p. 599). When bile salts are fed to an animal they can be recovered almost quantitatively from a biliary fistula. This indicates that in the intact animal the re-absorption of bile salts is almost complete (about 90 per cent). Under ordinary circumstances comparatively small amounts (about 10 per cent) of bile salts are formed afresh, i.e., their concentration in the bile is maintained largely as a result of their being circulated over and over again through the portal and biliary systems. Nevertheless, if the bile be prevented from entering the intestine by draining it to the exterior through the fistula, its concentration in bile salts does not become materially reduced. Berman and his associates found that, in dogs which lost all their bile through a fistula, about 0.5 gram of cholic acid was excreted in 8 hours. These facts indicate the existence of some unknown mechanism controlling bile salt production.

Tests for bile salts. Pettenkoffer's test. Five cubic centimeters of the fluid to be tested are mixed in a test tube with a few drops of a 10 per cent solution of cane sugar. A cubic centimeter or two of concentrated sulphuric acid are introduced beneath the surface of the mixture. The appearance of a red ring at the junction of the two liquids indicates the presence of bile salts; upon agitation the color diffuses through the solution. The color is due to the formation of cholalic acid from the bile acids and its combination with the furfural resulting from the decomposition of the cane sugar. A few drops of a 1 in 1000 aqueous solution of furfural itself may be employed (Mylin's modification) instead of the sugar solution.

Rowntree and associates have developed a method for the quantitative estimation of bile salts in blood based upon the Pettenkoffer reaction. The bile salts are extracted from the blood with alcohol and the test performed upon the extract. The color is compared in a colorimeter with that produced under similar conditions in a standard solution of pure glycocholic acid. The results are expressed in terms of glycocholic acid. Normal human blood contains from 2.5 to 6 mg. per cent of bile acids. In obstructive jaundice the value is increased, sometimes several fold.

Hay's test is based upon the property of the bile acids to lower surface tension (p. 462).

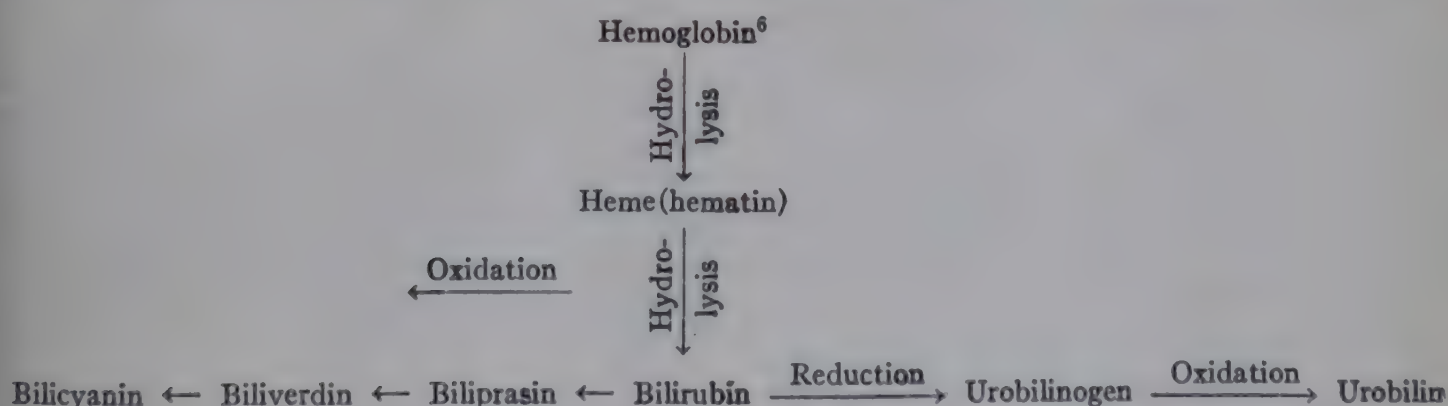
The bile pigments

The biliary pigments are *bilirubin* and *biliverdin*. Bilirubin ($C_{43}H_{66}N_4O_6$) is the chief pigment in human bile and in the bile of the carnivora. Biliverdin ($C_{43}H_{66}N_4O_6$) is an oxidative derivative of bilirubin and is present only in small amounts in human bile but is the chief pigment of birds'

bile. The pigments constitute from 15 to 20 per cent of the total solids in liver bile.

The readiness with which the bile pigments are oxidized and the color changes which they undergo in the process are the basis for Gmelin's test for bile in body fluids. If, for example, a fluid containing bile be passed through filter paper, and a drop of fuming nitric acid be then dropped upon the wet surface of the filter, the pigment is oxidized and a series of concentric rings of different colors appears—yellow, yellowish-red, violet and blue-green from within outwards. Besides biliverdin other derivatives of bilirubin are found in the body. *Urobilinogen* (cf. below and p. 460) is a reduction product of bilirubin; upon oxidation it yields *urobilin*. *Bilicyanin* and *bilifuscin* are formed by the oxidation of biliverdin. The latter two pigments are not found in bile but may be present in gallstones. *Biliprasin* is an intermediate product formed in the oxidation of bilirubin to biliverdin.

THE ORIGIN OF THE BILE PIGMENTS. Bilirubin is derived from hemoglobin, being the porphyrin (globin-free and iron-free) fraction of the hemoglobin molecule (p. 40). Any condition which leads to an increased destruction of red cells (hemolysis) causes a greater production of bile pigment. The chemical relationship between hemoglobin and the various bile pigment derivatives is shown schematically below.⁶



THE SITE OF BILIRUBIN FORMATION has been a subject of controversy for many years and it is only recently that the question has been answered definitely. The discovery, in old extravasations of blood, of a pigment with the chemical properties of bilirubin, was one of the first observations to throw doubt upon the view then prevailing, namely, that the liver was solely responsible for bile pigment formation. This pigment was called

⁶ Lemberg's researches point to a different sequence of chemical changes. He finds that hemin (derived from hemoglobin, p. 40), first yields biliverdin which then undergoes reduction to bilirubin.

⁶ Myoglobin (p. 43) and possibly pigment constituents of the diet may also as a source of bilirubin.

hematoidin (Virchow); the significance of its discovery lay in the fact that the old blood clots in which it was found were in situations remote from the liver. Hepatectomy in geese—which is a relatively simple operation on account of the anatomical peculiarities of the avian liver—was performed by Minkowski and Naunyn with the object of finding a definite answer to the question of the site of bile pigment production. Arseniuretted hydrogen, a powerful hemolytic poison, when injected into normal birds caused the accumulation of bile pigment in the blood. No such effect followed injection of the poison into hepatectomized birds. This apparently crucial experiment indicated that the liver alone was capable of forming bile pigment. McNee some years later repeated this experiment and obtained the same results, but he suggested that the reticulo-endothelial elements of the liver (Kupffer cells) rather than the true secretory cells were responsible. Investigations upon this subject within more recent years have proved conclusively, however, that in mammals the liver is not essential for bile pigment formation. Whipple and Hooper, employing dogs, attempted to isolate the liver from the general circulation. Bilirubin was found in excess in the circulating blood, a result diametrically opposed to the results obtained with

birds. The method employed by these investigators for the isolation of the liver has been criticized, but nevertheless the conclusion which they reached, namely, that tissues other than the liver have the ability to produce bile pigments has been substantiated by Mann, Bollman and Magath, and is now universally accepted. These observers removed the liver completely from dogs (p. 287). The animals survived for 24 hours or more; bilirubin commenced to appear in the blood in from 3 to 6 hours after the operation⁷ and gradually increased in amount up to the time of

⁷ Dog's plasma normally does not contain appreciable amounts of bilirubin.

death. The injection of hemoglobin into the circulation increased the bile pigment accumulation. Mann and his associates also showed by spectroscopic methods that the blood of the splenic vein of a normal animal has a higher bilirubin concentration than that in the corresponding artery.

It is now accepted that the elements of the *reticulo-endothelial system* (see p. 78) situated in various parts of the body, spleen, lymph glands, bone marrow and the general connective tissues, as well as in the liver, are responsible for the formation of bile pigment. Of these, the bone marrow is probably the most important. In an animal deprived of both spleen and liver, bilirubin continues to be formed at approximately the normal rate.

A certain amount of bilirubin is normally present in human serum, (from 0.2 to 0.8 mg. per 100 cc.) as a result of the transformation by the reticulo-endothelial elements of hemoglobin liberated from broken down red cells (p. 56). It has been estimated that 1 gram of hemoglobin yields 40 mg. of bilirubin. The iron which is freed from the hemoglobin is stored mainly in the liver (p. 58) but also to some extent in the spleen. It has been shown by Rich that the hemoglobin-bilirubin transformation effected by the reticulo-endothelial structures is an intracellular process. When fresh red cells were cultured with the reticulo-endothelial cells the former were destroyed, and in a short time typical crystals of bilirubin, and in some cases biliverdin, were found to have formed within the phagocytes. In some instances iron deposition within the cells and adjacent to the crystals could be detected by means of the Prussian blue reaction.

The results of the earlier experiments of Minkowski and Naunyn are explained in the light of these discoveries. The reticulo-endothelial system of the bird is practically confined to the liver. When the liver was excised all the cells capable of forming bile pigment were therefore removed.

There is no evidence that the true secretory cells of the liver play any part in the formation of bilirubin. They merely excrete the pigment that reaches them preformed.

UROBILINOGEN, UROBILIN; THE CIRCULATION OF BILE PIGMENT. The bilirubin that enters the intestine undergoes reduction by bacteria to form *urobilinogen* (also called *stercobilinogen*). A part of this is excreted in the stools and by oxidation is converted to *urobilin* (*stercobilin*). The latter can be detected spectroscopically or by the green

fluorescence which it gives with a solution of alcoholic zinc acetate. A certain proportion of the urobilinogen is reabsorbed into the portal circulation, passes to the liver, and is almost completely re-excreted in the bile (fig. 197). Any urobilinogen which may escape into the general circulation and be excreted by the kidney becomes oxidized to *urobilin* after the urine has been voided. Normally, however, no urobilin or mere traces (0.5 to 2 mgm.) appears in the urine. Bilirubin itself does not appear normally in the urine, so the color of urine is due to neither of these pigments (p. 398). That the urobilinogen normally present

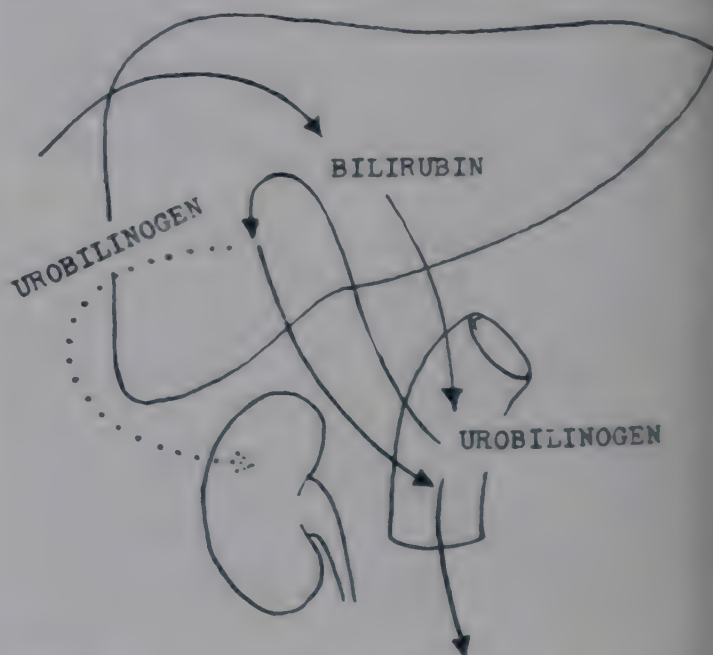


FIG. 197. Diagram illustrating the formation of urobilinogen from bilirubin in the intestine, its excretion in part in the feces and its absorption in part into the portal blood. Normally, the absorbed pigment except in negligible amounts is practically all re-excreted in the bile. The dotted lines indicate its passage into the blood, and its excretion by the kidney in cases of liver damage, excessive blood destruction or in the early stages of obstructive jaundice.

in bile merely represents re-excretion of this pigment after its absorption from the intestine was clearly shown by Elman and McMaster. When the entire output of bile was collected through a fistula (i.e., none was allowed to enter the intestine) there was complete disappearance of urobilinogen from the bile after the pigment already present in the intestine had been carried away in the feces. The fistula bile remained free from urobilinogen unless infection of the biliary tracts had occurred, under which circumstance bacterial action in these situations caused its formation. When a part of the bile was allowed to enter the intestine or bile was fed by mouth the derived pigment invariably appeared in the fistula bile.

Also, complete experimental obstruction of the

common bile duct, since it prevented the re-excretion of the urobilinogen absorbed from the intestine, resulted in its accumulation in the blood and its excretion in the urine. These effects however, can only occur for a short time after the duct has been obstructed, and are due to the absorption of pigment remaining in the intestine from the period prior to obstruction. After the pigment has been cleared from the intestine, the urine, though it may contain large amounts of bilirubin, is quite free from the derived pigment. Depression of the excretory function of the liver by such poisons as chloroform, phosphorus, etc. caused urobilin to appear in the urine, even though the injury was slight and there was no bilirubinuria. When bilirubin formation was increased by hemolytic agents urobilinogen production was also increased; the liver even though its function was normal was unable to re-excrete the excess pigment absorbed from the intestine, and urobilin appeared in the urine.

Urobilinogen is in rare instances formed in situations other than the intestinal tract and independently of bacterial action. Rabinowitch, for example, has reported a case in which large quantities of urobilinogen were present in the urine. A sterile ovarian cyst containing an old blood clot and a high percentage of urobilinogen was revealed by operation. When the cyst was removed the urobilinogen disappeared from the urine.

Lecithin and cholesterol

Lecithin is present in human liver bile to the extent of from 0.02 to 0.05 per cent. The *cholesterol* content is normally from 0.04 to 0.16 per cent. The cholesterol is present in the free state, i.e., not in the form of esters. The percentages of these materials in the bile of the gall-bladder is, as a result of the absorption of water and salts through the gall-bladder mucosa, much higher than the percentages in liver bile. The ratio of the concentration of cholesterol in bile to that of the bile salts is from 1:20 to 1:30. The ability of the bile to hold cholesterol in solution is in large degree dependent upon the bile salts. If the ratio falls to 1:13 precipitation of cholesterol occurs. Andrews and associates showed that if bile be dialysed against water, bile salts are removed and the bile becomes turbid as a result of cholesterol precipitation. The importance of this observation in relation to gallstone formation is considered on page 467. The fatty acid concentration of the bile is of as great if not greater importance than the bile salt concentration in

holding cholesterol in solution. Little is known concerning the origin and function of the biliary cholesterol. It may be derived from the stroma of disintegrated red cells or from nervous tissue, which of course contains it in large amounts. According to Gardner the cholesterol of the bile does not vary with changes in the total blood cholesterol, nor is its concentration raised by increasing the cholesterol content of the diet; it continues to be excreted upon a cholesterol-free diet. A biliary-portal circulation of cholesterol has been shown to occur, i.e., excretion in the bile, re-absorption from the intestine and re-excretion by the liver.

THE FUNCTIONS OF THE BILE

Besides serving as a vehicle for the excretion of pigments and certain other waste products from the body, the bile performs important functions in the intestine.

The rôle of the bile in fat digestion

Bile is essential for the efficient digestion of fat by the pancreatic and intestinal juices, yet the bile itself contains practically no lipase or indeed any other digestive enzyme. The absence of any lipolytic action on the part of the bile is illustrated by the observation of Claude Bernard made upon the lymph vessels of the rabbit's intestine at the height of digestion. In this animal the pancreatic duct opens into the intestine 10 cm. or so below the orifice of the bile duct. After a meal the lymph vessels in the intervening area were quite clear, but those below the pancreatic duct were milky with absorbed fat. The importance of bile, nevertheless, in fat digestion (and absorption) was shown by the following experiment. When the orifice of the bile duct in the dog was transplanted into the intestine a short distance *below* the pancreatic duct the lymph vessels in the space separating the ducts were free from fat, while those below the transplanted bile duct were milky. The coadjutant action of the bile upon fat digestion is also shown by the fact that, if the bile is prevented from entering the duodenum, either by experimental ligation of the common bile duct in animals, or in man as a result of obstruction of the duct by a stone or by its obliteration in any other way, fat digestion is imperfect, a proportion of the fat of the food being excreted unchanged in the feces. The important aid which bile lends to the digestion of fat is due to the bile salts. The influence of the bile salts is exerted in two ways.

First, they aid emulsification to a marked degree, the fat globules are reduced in size, and in consequence, a finer and more stable emulsion results. In this way the total surface area of the fat exposed to the action of pancreatic lipase is enormously increased. This action depends mainly upon the property possessed by the bile acids of lowering surface tension. Upon this property is based Hay's test for the detection of bile in urine. Flowers of sulphur float upon the surface of normal urine but sink if bile be present. The bile salts have also a *hydrotropic action*, i.e., they render water-insoluble materials such as fatty acids and calcium soaps readily soluble in the watery fluids of the intestine. Some of these fatty acids when free in solution aid the emulsification process since they too have the property of lowering surface tension. Their combination with alkali to form soaps—the extent to which this occurs being dependent upon the reaction of the intestinal contents—also, and for the same reason, furthers emulsification. The cholesterol of the bile acts as an adjuvant to the bile salts in the emulsification process.

Secondly, the bile salts (by virtue of the cholic acid radical) act as specific activators of pancreatic lipase; the latter enzyme has only a weak action in their absence. They also act in a similar manner, though to a less degree, upon gastric lipase, have no effect apparently, upon the fat-splitting enzyme of the intestinal juice. That this action of bile is distinct from its effect in furthering emulsification is shown by the fact that the hydrolysis by pancreatic lipase of triacetin, which is *soluble* in water, is also accelerated by the bile salts.

The rôle of bile in fat absorption

Fat digestion although seriously impaired may be carried on to a considerable extent in the intestine after removal of the pancreas and ligation of the bile duct; the lipase of the intestinal juice is then chiefly responsible for the cleavage of the fat molecule. Gastric lipase, especially if the intestinal contents are definitely acid in reaction, may also aid to some extent. Certain bacteria in the colon have a lipolytic action and they may account for a considerable quantity of fat being split in the large intestine. In obstruction of the bile ducts alone the greater proportion of the fat is split, over 80 per cent of the fecal fat being in the form of fatty acids. The *absorption* of fat, on the other hand, is very greatly interfered with under these circumstances, only a small proportion of ingested fat being utilized. Bile is therefore of much greater importance for fat absorption than for fat digestion. According to Verzár the fatty acids unite with the bile salts to form com-

plex compounds; as such the greater part of the fat is absorbed from the intestine.

The solvent action of the bile salts upon cholesterol has been mentioned (p. 461). Bile is also necessary for the absorption of vitamin D; the essential constituents for this action being, apparently, the bile salts. Graeves and Schmidt found that the calcium balances of dogs with biliary fistulae became negative but were restored to normal by the subcutaneous injection of vitamin D. Taylor, Weld and Sykes noted that a rise in the serum calcium could not be induced in dogs with biliary fistulae by the oral administration of irradiated ergosterol but that this substance exerted its usual effect when given intravenously, or by mouth if combined with bile or bile salts (see also p. 466). With regard to the other fat-soluble vitamins, vitamin K and probably vitamin E also fail to be absorbed in adequate amounts in the absence of bile. Bile is necessary for the absorption of carotene though not for vitamin A itself.

OTHER FUNCTIONS have been ascribed to the bile, but they are based upon a less sure foundation than those that have been discussed. Among these are (a) *antiputrefactive*. This action is probably secondary in nature and not due to any direct inhibitory effect of the bile upon bacterial growth. Indeed it has been shown that bile will serve as a suitable culture medium for microorganisms, and the contents of the gall-bladder apparently are readily infected. However, in the absence of the bile putrefactive processes in the intestines are no doubt more active, but this is probably due to the protective covering which the undigested fat affords for protein material; the growth of proteolytic bacteria is thereby encouraged. (b) *Laxative*. Bile when introduced directly into the rectum or colon stimulates peristalsis. It is also stimulating to the movements of the small bowel, but the constipating effect which follows the exclusion of bile from the intestine is probably brought about mainly indirectly, the unsplit fat inhibiting intestinal motility. (c) Bile appears to possess a function apart from all those mentioned which is essential to life. Whipple found that bile fistula dogs develop abnormalities of the bones, associated with a loss of inorganic constituents. They eventually succumb unless bile is fed.

THE SECRETION OF BILE

It will be recalled that the secretion of bile by the polygonal cells of the liver and its passage along the biliary channels for storage in the gall-bladder is a continuous process. The intermittent discharge of bile from the gall-bladder will be considered in Chapter XLII. Several substances

stimulate biliary secretion. Materials which act in this way are known as *cholagogues*.⁸ The natural and the most powerful excitants of biliary secretion are the bile salts themselves. *Secretin* is also a physiological stimulus of biliary secretion (p. 451). Meat or fat in the diet stimulates the flow, whereas sugar is inhibitory. In starvation the volume of the secretion is reduced by about half. Drugs such as podophyllin, aloes, acids and several other chemicals which have enjoyed a reputation as cholagogues, were found by Whipple and his associates to have no notable effect upon biliary secretion. Calomel and ammonium chloride are without any significant effect, but salicylates and linseed oil are definitely stimulating. Adrenaline decreases the flow, whereas pilocarpine and prostigmine increase it. The rate of secretion in man (bile fistula) on an ordinary diet averages around 23 cc. per hour during the waking hours and 15 cc. per hour in sleep—a total volume of around 500 cc. daily.

The bile is capable of being secreted under a pressure of from 250 to 300 mm. of water. If a manometer be placed in the common duct the secretion of bile ceases when the pressure reaches this height and shortly afterward jaundice appears. Under ordinary physiological conditions the sphincter surrounding the opening of the common duct into the duodenum is kept tonically closed. The duct system fills with bile and when the pressure rises to from 50 to 70 mm. H₂O the fluid passes along the cystic duct into the gall-bladder. As a result of the pressure-regulating function of the gall-bladder (p. 473) the maximal pressure in the biliary canal system is not attained after obstruction of the common duct in animals until a considerable time has passed. Mann found that jaundice did not develop after this operation in dogs until the lapse of from 48 to 72 hours.

Bile secretion is under vagal control, stimulation of the peripheral end of the vagus (in dog or monkey) causing a very definite increase in bile production (Tanturi and Ivy). Snyder found that an acetylcholine-like substance appeared in the hepatic veins upon vagal stimulation. A reflex secretory effect can also be demonstrated by

⁸ This is a very old term dating from the time of Galen and refers to increased flow of bile into the intestine which, of course, may be due either to increased secretion or to discharge from the gall-bladder. It has been suggested recently that the word cholagogue be used to indicate a stimulating action upon the discharge of bile from the gall-bladder, and the term *choleresis* to denote increased secretion by the liver.

stimulating the central cut end of one vagus. Bile secretion is inhibited reflexly by distension of the colon and by stimulation of the sympathetic. This latter effect is probably secondary to a constrictor effect upon the hepatic vessels. The vagus in the dog also contains some fibers which inhibit secretion. There appears also to be a psychic secretion of bile.

JAUNDICE

DEFINITION AND CLASSIFICATION

When bile pigment is present in excessive amount in the blood (hyperbilirubinemia) it escapes into the tissues, e.g., skin, mucous membranes and conjunctivae which then become stained a yellow tint. The condition is termed *jaundice* or *icterus*. The bilirubin appears in the urine and sweat but does not pass into the saliva or milk, nor as a rule into the cerebrospinal fluid.⁹ Jaundice may be due to the production of bile pigment in excess of the amount with which the excretory power of the normal liver can cope. Or, it may result from the failure of a damaged liver to excrete the bilirubin produced in normal amounts. In either case bile pigment accumulates in the blood and when it reaches a certain degree of concentration diffuses into the tissues to give the characteristic discoloration. Jaundice may therefore be divided into two main groups corresponding to the mode of its production. These are, the *hemolytic* and the *hepatic*, the former resulting from increased production of pigment, and the latter from depressed or suppressed excretion of pigment by the liver. In the hepatic form the retention of pigment may be due to (a) obstruction of the bile passages or (b) damage of the liver cells by toxic agents or infections. Jaundice is also sometimes classified into obstructive and non-obstructive, the latter being subdivided into hemolytic, on the one hand, and toxic or infective on the other. These principal varieties of jaundice are tabulated below.

Hepatic	1. Hemolytic jaundice	} non-ob- structive
	2. Toxic, or infective jaundice	
	3. Obstructive jaundice	

HEMOLYTIC JAUNDICE

It has already been mentioned that a small amount of bile pigment (0.2 to 0.8 mg.) per cent

⁹ Its appearance in the cerebro-spinal fluid is not uncommon in children.

is present in normal human serum and that any condition which increases red cell destruction also increases the formation of bile pigment. Unless the over-production of bile pigment is very great the healthy liver, which possesses a large functional reserve, is able to meet the extra demand, but when the disintegration of red cells is such that the balance between production and excretion of pigment cannot be maintained even by the normal liver, the bilirubin concentration in the blood rises above the normal limits. *Hemolytic agents* of all sorts, such as the toxins of certain infections, septicemia, etc., and various chemical poisons may induce icterus (p. 49) of this type. It also occurs to some degree in such states as *pernicious anemia*, *malaria*, etc., in which blood destruction is a pronounced feature. It may be produced in animals by the injection of such hemolytic poisons as toluylendiamine and arseniuretted hydrogen. The disease known as *acholuric jaundice* which tends to run in families and is associated with splenic enlargement and increased fragility of the red cells (p. 61), is of this type. Jaundice in the new-born, *icterus neonatorum*, (*benign*) frequently occurs as a slight transient staining of the skin and is most probably the result of the destruction of the red cells that are in excess at birth (p. 8). It is perfectly innocent and indeed may be considered physiological. It does not appear until a day or two after birth and lasts for five or six days.

OBSTRUCTIVE JAUNDICE

Obstructive jaundice results from blockage of the hepatic or common bile duct by (a) a gallstone or parasites within its lumen, (b) compression of the duct by a tumor (e.g., in head of pancreas) or occlusion of its opening into the duodenum, (c) congenital obliteration of the ducts (a fatal form of *icterus neonatorum*).

In complete biliary obstruction the stools are clay-colored; urobilinogen (p. 460) is absent from the feces and urobilin from the urine. The jaundice resulting from obstruction is not due to the re-absorption into the blood or lymph vessels of bile which has been secreted into the obstructed passages, but to the suppression of secretion. After obstruction, secretion continues only for a short time, or until the pressure in the ducts equalizes the secretory pressure of the liver cells (250 to 300 mm. H₂O). In obstructive jaundice the bile pigment is believed to pass from the blood into the liver cells, but instead of being secreted into the bile capillaries, it is absorbed into the

hepatic veins and lymphatics. McMaster and Rous found, for example, that when obstructive jaundice was induced in dogs, the occluded duct after a time became filled with a fluid free from pigment and bile salts—the so-called *white bile* (p. 472). According to these observers the colorless fluid is secreted by the membrane lining the ducts.

The excretory mechanism of the liver has been shown by McMaster and Rous to possess a large reserve since, in the dog, jaundice does not develop until from 90 to 95 per cent of the excretory ducts have been occluded.

TOXIC AND INFECTIVE JAUNDICE—LIVER DAMAGE

Liver damage and consequent depression of secretory functions of the liver may be produced by: (a) various *poisons*, e.g., arsphenamine, phosphorus, chloroform, etc., (b) *acute and chronic liver diseases*, e.g., acute yellow atrophy, cirrhosis, inflammation of the bile passages (catarrh, jaundice, suppurative cholangitis); (c) *toxins* of various pathogenic bacteria; (d) engorgement of the hepatic vessels as a result of *cardiac failure*. It has been pointed out by Meakins that in the latter condition the edema or ascitic fluid does not contain bilirubin and the skin over edematous regions is not stained. There is no explanation of this fact.

Jaundice is frequently due to a combination of causes.

It should be pointed out that in any given case of jaundice two or all three causative factors may and frequently do, coexist. Blood destruction alone, according to Rich, is not capable of producing jaundice except perhaps in rare instances when the hemolytic process is of extreme degree. In pernicious anemia, for example, there is an associated hepatic insufficiency and even in the ordinary icterus of the new-born the immaturity of hepatic function is claimed to be a factor; also many hemolytic substances are liver poisons as well. In obstructive jaundice the liver cells suffer damage from pressure and the retention of bile salts probably induces a certain amount of hemolysis. Furthermore, in many inflammatory conditions of the bile ducts an obstructive element (due to plugging of the intra-hepatic ducts by the so-called *bile-thrombi*) exists in conjunction with the hepatic damage. In the jaundice of cardiac diseases the hepatic engorgement produces obstruction of the finer bile capillaries as well as injury to the liver cells through anoxemia. The occurrence of infarcts in the lung is also a factor.

some cases; bilirubin production is increased through the break-down of red cells in the infected areas.

CLINICAL TESTS EMPLOYED IN THE STUDY OF JAUNDICE

The van den Bergh reaction

This test—a modification of Ehrlich's diazo reaction—is employed for the detection of bile pigment in blood serum. There are two main types of the reaction—the *direct* and the *indirect*. The direct reaction occurs without the addition of alcohol, which is essential for the indirect reaction.

The REAGENTS used in the test are:

Solution A:

Sulphanilic acid.....	0.1 gram
Concentrated HCl.....	1.5 cc.
Water up to.....	100 cc.

Solution B:

Sodium nitrite.....	0.5 gram
Water.....	100 cc.

To perform the test 10 cc. of solution A and 0.3 cc. of solution B are freshly mixed. This mixture is used as the reagent in both forms of the test.

The *direct reaction* is that which follows the addition of 1 cc. of the reagent to 1 cc. of serum. It may occur in one of three forms, (a) *immediate* or *prompt*; a violet color due to the formation of diazo-bilirubin develops from 20 to 30 seconds. (b) *Delayed reaction*; no change appears until a minute or more has elapsed, when a reddish color develops which gradually deepens to violet. (c) *Bi-phasic*; a red color appears promptly in (a) but takes a variable length of time to change to violet.

The *indirect reaction* is carried out as follows. One cc. of serum is mixed with 2 cc. of 95 per cent alcohol. After shaking and centrifuging, to 1 cc. of the supernatant fluid, 0.25 cc. of the reagent mixture and 0.5 cc. of alcohol are added. A reddish-violet color develops almost immediately.

Normal bile and the serum in obstructive jaundice give the prompt direct reaction. Normal serum, the serum in hemolytic jaundice and the bilirubin formed from old blood extravasations into the connective tissues, serous cavities, etc., give only the indirect reaction. The sera in types of jaundice due to liver damage give a direct reaction (usually of the delayed or biphasic type) and sera which give the direct reaction also give the indirect.

The indirect reaction is used as the basis for the quantitative estimation of bilirubin in all types of sera. The serum after the color reaction has developed is compared in a colorimeter with a standard solution made by dissolving 2.161 grams of anhydrous cobaltous

sulphate in 100 cc. of distilled water. The color of this standard corresponds to that developed by 1 unit of bilirubin. A *unit* is defined by van den Bergh as 1 part of bilirubin in 200,000 parts of serum. Normal serum contains from 0.4 to 1.5 unit (i.e., bilirubin is present in a dilution of 1 part in from 500,000 to 100,000 parts of serum, or from 0.2 to 1.0 mg. per 100 cc.). In the quantitative estimation of bilirubin in sera showing the direct reaction the method has been rendered more accurate by the modification of Thannhauser and Anderson. This consists in first adding 0.5 cc. of the reagent to 1 cc. of the serum, and a minute or two later 2.5 cc. of alcohol and 1 cc. of a saturated solution of ammonium sulphate. By adding the diazo-reagent before the alcohol the loss of bilirubin which results from its being carried down with the albuminous precipitate is avoided. When the alcohol is added later the diazo-bilirubin compound is not thrown down but remains in the supernatant fluid.

The quantitative van den Bergh reaction is of value in the detection of latent jaundice, i.e., a hyperbilirubinemia which has not reached the level at which jaundice appears, and in recording the progress of a case of manifest jaundice.

The icteric index

The bile pigment concentration may also be estimated by comparing the color of the serum with that of a standard solution. A sample of blood is allowed to clot; after centrifuging, 5 cc. of serum are pipetted off and the color of the sample compared in a colorimeter with a 1 in 10,000 solution of potassium bichromate. The colorimeter is set at 15 mm. for the standard solution. This number is divided by the number on the serum scale when the color of the serum and of the standard solution match. The result is called the *icteric index*. Thus if the reading of the serum scale is 3 the icteric index is 5.

Galactose tolerance test of liver function

Galactose is converted into glycogen (though with considerable difficulty) by the normal liver. This sugar is therefore used as a test to distinguish jaundice due to obstruction from that primarily due to liver damage. The patient is fasted for 12 hours and then given 40 grams of galactose in 500 cc. of water. Normally or in jaundice of the obstructive type 3 grams or less are excreted in the urine within 5 hours. In jaundice due to liver damage the excretion amounts to from 4 to 5 grams or more during the first 5 hours.

THE FEATURES IN DIFFERENT TYPES OF JAUNDICE COMPARED

In obstructive jaundice and in jaundice resulting from liver damage, the staining of the skin, mucous membranes and urine with bilirubin tends

to be much more pronounced than in the hemolytic type. Except for a short time after the duct has been obstructed urobilin is absent from the urine and urobilinogen from the feces (p. 460). The plasma phosphatase (p. 717) is increased in jaundice due to obstruction or to liver damage but not in the hemolytic type. In obstructive jaundice the effects, e.g., *bradycardia*, *itching of the skin* (*pruritus*) and *reduced coagulability of the blood* referable to the retention of biliary constituents other than pigment may be evident. The cardiac slowing has been attributed to the action of the bile salts, though proof is lacking. Since the bile acids are conjugated in the liver it is not to be expected that their concentration in the blood will be raised in a purely hemolytic type of jaundice; this is found to be the case. On this account the latter type is sometimes spoken of as "dissociated jaundice." Also in severe liver damage bile acids may be absent from the blood though the hyperbilirubinemia is pronounced. In other instances of relatively mild degrees of hepatic insufficiency a converse type of "dissociated jaundice," namely, increased concentration of bile acids in the blood without icterus, is sometimes seen.

The bleeding tendency in obstructive jaundice is a serious hazard should a patient be required to undergo surgical treatment. Only within recent years, as a result of the work of Roderick, of Quick and his associates, and of Dam, has the cause of the prolonged coagulation time been discovered. It is due to prothrombin deficiency, which is the result in turn of a virtual lack of vitamin K (p. 90); in the absence of bile from the intestine the vitamin is not absorbed in adequate amounts. The oral administration of vitamin K with bile salts corrects the hemorrhagic tendency. Possibly an additional though minor factor in the lengthened coagulation time is the retention in the blood of certain organic sulphur-containing compounds (e.g., cysteine and taurine) possessing anticoagulant properties (Carr and Foot). Jaundice due to liver damage is also sometimes associated with a prolonged bleeding time and is then possibly due to the incapacity of the liver to manufacture the antihemorrhagic vitamin from a precursor in the diet. The cause of the pruritus in obstructive jaundice is unknown. Rowntree and associates found that though a high concentration of bile acids in the blood was frequently associated with pruritus this may occur with a normal bile-acid concentration or be absent when the latter is high.

In the non-obstructive types of jaundice (hemolytic, or those due to liver damage) urobilin may appear in the urine, and in the hemolytic types the excretion of urobilinogen in the feces is increased. The different van den Bergh reactions, namely, the direct in the obstructive and liver injury types of jaundice and the indirect in the hemolytic type are believed to depend upon some physical or chemical difference between the serum bilirubin in the two instances. It has been supposed that the differences depend upon whether or not the pigment has passed through the liver cells. In the obstructive and liver injury types (direct reaction) the pigment apparently takes this course. In the hemolytic type (indirect reaction), on the other hand, the retained bilirubin is that which the liver cannot dispose of and probably therefore does not enter the secretory cells. Several theories have been put forward in attempts to explain the difference in behavior of the two types of bilirubin toward the diazo-reagent. According to one view, the pigment giving the indirect reaction is combined with or adsorbed to some colloidal constituent (protein or lipid) of the serum which prevents it coupling with the diazo-reagent; alcohol is required to break the union. The direct reaction on the other hand, is due to bilirubin in the free state. It is suggested further that some substance supplied by the liver cells, possibly bile salts, is capable of breaking the union, thus accounting for the direct reaction given by normal bile and by the serum in obstructive jaundice.

Another explanation (Collinson and Fowweather) is based upon the view that bilirubin is an acid possessing two carboxyl groups. The direct reaction, it is claimed, is due to bilirubin in the form of an alkali salt (probably an ammonium salt or, according to Hunter, a monosodium salt). The alkali salt, being water-soluble, is able to react with the diazo-reagent. The indirect reaction, on the other hand, is due to the acid pigment itself which is insoluble in water but soluble in alcohol; the reaction between the diazo-reagent, which is also soluble in alcohol, can therefore take place. According to this view the bilirubin as formed by the reticulo-endothelial elements is conveyed to the liver cells where normally, or in obstructive jaundice, it is converted to the alkali salt.

Some of the differences between the properties of the two forms of bilirubin and certain observations relevant to the foregoing discussion are given below.

(a) The bilirubin of serum which gives the indirect reaction is oxidized less readily than that which gives the direct reaction (van den Bergh).

(b) The bilirubin giving the direct reaction is not extractable with chloroform, whereas the pigment giving the indirect reaction can be readily extracted by means of this reagent (Grunenberg).

(c) Serum giving the direct reaction gives the indirect reaction after heating for a short time (van den Bergh).

(d) The bilirubin in obstructive jaundice as shown by Blankenhorn and Hoover dialyses through a colloidion membrane, whereas the pigment of hemolytic jaundice does not. This observation is in accord with the fact already mentioned that the pigment in obstructive jaundice passes more readily into the tissues and urine than does that of the hemolytic type. In the former, staining of the skin and urine occurs when the serum concentration reaches 4 units (i.e., 1 part in 50,000 or 2 mg. per 100 cc.), whereas in the hemolytic type the concentration of bilirubin in the blood may be much higher than this without manifest jaundice.

(e) It has been shown by Barron that when a solution of pure sodium bilirubinate, which gives a direct reaction, is added to normal serum an indirect reaction is obtained. If, however, bile salts, sodium oleate or cholesterol be added to the serum together with the bilirubin the reaction becomes direct.

(f) When the bile salt concentration in the blood is elevated the serum may give a direct reaction though the serum bilirubin is within normal limits.

GALLSTONES—CHOLELITHIASIS

Gallstones are composed of constituents of the bile which have been thrown out of solution. Cholesterol is present in greater or less amounts in the commoner varieties of gallstone. Some stones may be composed almost entirely of this substance. In other types of stone, bile pigment or calcium is an important or the predominant constituent. Gallstones therefore differ considerably in size, color and inner structure according to the materials of which they are composed. They are classified according to their compositions into "pure" cholesterol, cholesterol-pigment-calcium, "pure" bilirubin, bilirubin-calcium and calcium carbonate stones. The latter are very rare in man but not uncommon in cattle. The "pure" cholesterol stone contains from 90 to 98 per cent of cholesterol, the remainder being made up of calcium, bile pigments, protein, etc. The "pure" pigment and the bilirubin-calcium stones, on the other hand, contain varying amounts of cholesterol. The cholesterol-pigment-calcium stone is the commonest variety. Stones of this type are usually multiple and, as a result of pressure of

one stone against another, show numerous facets upon their surfaces. They contain about 80 per cent of cholesterol which is deposited in cream-colored layers alternately with darker bilirubin-calcium laminae. The great majority of stones are formed in the gallbladder, but they may also form in the hepatic duct or even in the smaller ducts within the liver.

The formation of gallstones

The mechanism of gallstone formation is not clearly understood but the following are recognized as being the most important factors to be considered: (a) *Injury, especially of an infective nature to the gall-bladder wall*, (b) *disturbance in cholesterol metabolism*, (c) *stasis of the bile*, and (d) *reaction of the bile*.

(a) **INFECTION.** Following the classical work of Naunyn infection was looked upon as the main, if not the only, cause of gallstone formation. Naunyn maintained, and it is now current teaching, that the cholesterol of the bile was not dependent upon the cholesterol level of the blood and could not be altered by diet. He also claimed, however, that abnormalities of cholesterol metabolism played a minor rôle in the production of gallstones. The mucosa of the gall-bladder, he believed, normally secreted cholesterol and calcium and the secretory process was stimulated by any local inflammatory state. Experiments in which human cholesterol stones were shown to be dissolved after a time in the gall-bladder of the dog under sterile conditions, but not if infection were present, the production of gallstones by injections of microorganisms into the circulation after injury to the gall-bladder, and the frequent occurrence of cholelithiasis after infective conditions, notably typhoid fever, were all taken to indicate that infection was essential for the production of biliary calculi. The solvent action of the bile salts upon cholesterol was also held to support this view and to be against the suggestion that this biliary constituent could be thrown out of solution in the absence of infection. It was argued that the bile as it came from the liver could never have so high a concentration of cholesterol that simple deposition could result, but that the cholesterol must be produced in excessive amounts by an inflamed gall-bladder in order to be precipitated. Of the normal concentrating power of the gall-bladder little was then known (see p. 471).

Though not denying the importance of gall-bladder injury and the production of cholesterol from the inflamed mucosa in many cases of cholelithiasis, Aschoff and others have insisted that these conditions are not essential to the formation of calculi, and that certain types, especially the solitary cholesterol stone (see below), can arise in sterile bile and in the absence

of any diseased condition of the lining membrane. This view is now generally accepted. Much of the earlier work upon cholesterol metabolism to which Naunyn pinned his faith has been proved to be erroneous.

The multiple cholesterol-pigment-calcium stones are usually looked upon as typical infection stones. They are laminated on cross section and have usually a frame-work of coagulated protein. These stones are often very numerous, sometimes numbered by hundreds, and an examination of their structure indicates that they have all been formed at about the same time. According to Aschoff, the starting point of their formation is the deposition of pigment in the form of fine rosette-like structures upon which coatings of cholesterol, pigment and calcium are subsequently laid. The inflammatory exudate is rich in protein material derived from the blood, as well as in cholesterol and calcium. The protein, it is pointed out, carries an electric charge of opposite sign to that held by the cholesterol, pigment and inorganic constituents of the bile. It is believed that as a result of these physico-chemical relations the deposition of cholesterol combined in varying degree with the other biliary constituents is effected.

(b) **METABOLIC.** The typical "metabolic" calculus is the large single stone of almost pure cholesterol—the *cholesterol solitaire*. This type of stone, according to Aschoff, is formed quite independently of infection or injury of any sort and is due to the crystallization of cholesterol out of a bile surcharged with this material. The common mixed stones (cholesterol-pigment-calcium) are also composed predominantly of cholesterol and probably in many instances are metabolic rather than infective in origin. In certain conditions, e.g., pregnancy, in which gallstones are prone to develop, the blood cholesterol has been said to be higher than normal (hypercholesterolemia) and there is evidence of a disturbance in cholesterol metabolism. But as a matter of fact, hypercholesterolemia, according to Gardner, is not common in pregnancy, the normal proportions of free cholesterol to cholesterol esters (cholesterol combined with fatty acids), however, are altered, the former being increased, the latter reduced. Abnormalities in cholesterol metabolism leading to such changes are probably of more importance in the production of gallstones than a rise in the total blood cholesterol. It has already been mentioned that a high blood cholesterol does not cause an increase in the cholesterol of the bile. Also, in certain forms of renal disease in which hypercholesterolemia exists there is little evidence that the latter leads to the production of gallstones; in other forms of renal disease the incidence of gallstones is higher than usual, yet hypercholesterolemia does not occur.

It has been mentioned that increasing the cholesterol of the diet does not raise the cholesterol concentration of the bile, so there is no logical reason, as pointed out by Gardner and associates, for excluding cholesterol-rich materials from the diets of those subject to cholelithiasis. Indeed, a high fat diet, by

stimulating gall-bladder contractions and so preventing undue concentration and stasis of bile, may exert beneficial effect.

The ratio of cholesterol in bile to the bile salts is an important factor in the formation of gallstones. The cholesterol-bile acid ratio in normal bile is between 1:20 and 1:30. Since neither bile salts nor cholesterol are absorbed under normal circumstances from the gall-bladder this ratio holds for both liver and gall bladder bile. According to Andrews, deposition of cholesterol occurs when the ratio falls to 1:13. He believes that infection, when it is a factor, plays its part in gallstone formation not so much through increasing cholesterol production as through reducing the bile salt concentration, for he claims that bile salts are absorbed through the inflamed gall-bladder mucosa. Dolkart and associates attach more importance to the concentration of fatty acids in the bile than to that of the bile salts in preventing the precipitation of cholesterol.

"Pure" pigment stones (they contain calcium and cholesterol as well) also occur apart from infection. They are small, and dark and, though usually occurring in the gall-bladder, may be found in the bile passages. Their origin is not clear, but since they often occur in conditions associated with an abnormally high bilirubin excretion, e.g., acholuric jaundice, they may be the result of the precipitation of bilirubin from a bile which contains excessive amounts of the pigment.

(c) **STASIS OR SLOWING OF THE BILIARY FLOW** within the bile passages may be responsible for the formation of small stones of pigment-calcium in these situations. When there is complete stasis, due to mechanical obstruction, the fluid in the larger bile passages contains none of the important biliary constituents. The so-called "white bile" fills the ducts and in consequence the formation of calculi is not possible (p. 472). Stasis of bile in the gall-bladder is an important factor in the production of gallstones in this situation.

(d) **REACTION OF THE BILE.** Until the work of Drury, McMaster and Rous this factor had received comparatively little attention. These observers caused gallstones composed, in varying proportions, of calcium carbonate, pigment and cholesterol to be formed in the bile of dogs which had their gall-bladders removed and their common ducts drained into a system of tubing. Encrustations of biliary constituents as well as more or less discrete calculi formed upon the walls of the tubing. These occurred under sterile conditions and in the absence of stasis. The deposits are claimed to result from the alkalinity of the liver bile. Normal bile of the dog as it flows along the bile passages was shown by Okada to be definitely alkaline while that of the gall-bladder was acid. Rous and his associates found the liver bile of dogs to have a pH of 8.20 or more, while after its stay in the gall-bladder its reaction became decidedly acid—pH 5.18 to 6.00. Bile from the human gall-bladder, though less alkaline than liver bile, has rarely a pH below 7.0. One of the functions

of the normal gall-bladder (p. 473) therefore appears to be the acidification of the liver bile. So long as this occurs in the usual manner the calcium carbonate of the bile remains in solution. In an alkaline bile, such as is collected from the common duct in the absence of the gall-bladder the calcium carbonate is thrown down, and with it the pigment and cholesterol constituents, to be deposited upon the walls of the delivery tubing. These observations suggest therefore that in any condition which interferes with gall-bladder function, e.g., infection, injury, or intermittent stasis, the usual acidification of the liver bile will not occur; calcium carbonate will then undergo spontaneous precipitation, and serve as a center or centers upon which the other biliary constituents become deposited.

AN ENUMERATION OF HEPATIC FUNCTIONS

Besides its secretory and excretory functions dealt with in this section the liver plays an important rôle in many other physiological processes. For the reader's convenience a list of these with page references is given below.

- (a) Blood formation in the embryo (p. 77); hematitic principle in the adult (p. 65).
- (b) Fibrinogen production (p. 4).
- (c) Prothrombin production (p. 90).
- (d) Heparin production (p. 89).
- (e) Iron and copper storage (pp. 58, 59).
- (f) Blood volume regulation (pp. 286, 625).
- (g) Reticulo-endothelial activity (Kupffer cells) (p. 80).
- (h) Detoxication (p. 507).
- (i) Protein metabolism, deamination (p. 544), amino-acid synthesis (p. 545), urea (p. 546), and uric acid (p. 565), hippuric acid synthesis (pp. 392, 546).
- (j) Carbohydrate metabolism (p. 572).
- (k) Fat metabolism (p. 601).
- (l) Heat production (p. 628).
- (m) Formation of vitamin A from carotene (p. 636).

The hepatic circulation is dealt with in Chapter XXVIII.

LIVER FUNCTION TESTS

Several of the specific functions of the liver have been utilized as tests for the investigation of the functional capacity of the liver as a whole, i.e., as a means of detecting the presence of hepatic damage and, in some instances, of gauging the extent to which such damage has occurred. Some of these tests will be very briefly described, the accounts being confined in the main to the general principles upon which the tests are based.

A. TESTS BASED UPON THE EXCRETORY FUNCTIONS OF THE LIVER

The quantitative van den Bergh reaction has been described (p. 465). Since the excretion of bilirubin is

an essential hepatic function a determination of the quantity of circulating bilirubin is a valuable means of estimating the extent of liver damage associated with jaundice, provided the hyperbilirubinemia is not the result of biliary obstruction or of blood destruction. The galactose tolerance test as a means of distinguishing jaundice due to liver damage from that due to obstruction has been described (p. 465).

The estimation of the quantity of *urobilinogen* excreted in the urine (p. 460) has also been employed as a test of liver function, but increased blood destruction, as in pernicious anemia, quite apart from liver damage will cause urobilinogenuria. Under such circumstances urobilin estimations obviously will give no information concerning liver function. Also, infection of the biliary passages may increase the urobilinogen output out of all proportion to the reduction of liver function.

Other tests based upon the excretory function of the liver are the *bromsulphalein*, *bilirubin* and *rose-bengal* tests. In each of these tests the respective material is injected intravenously and the rate of excretion estimated from the quantity retained in the serum after the lapse of a specified time; the concentration of the material in the serum is determined colorimetrically. These three substances are excreted practically entirely by the liver and no significant amounts are taken up by the reticulo-endothelial cells. In normal persons practically no retention of bromsulphalein (5 mg. per kilogram of body weight injected) after 30 minutes, or of bilirubin (1 mg. per kilogram of body weight injected) is observed at the end of 4 hours. In the case of rose-bengal (10 cc. of 1 per cent solution injected without regard to subject's weight) 50 per cent or more disappears from the serum within 8 minutes after the injection. These tests, like the van den Berg test, will of course be of no value if obstruction of the bile ducts exists; obviously, whether damaged or not the liver cannot then excrete the injected substances. Colorimetric difficulties also render the dye tests inapplicable in the presence of hyperbilirubinemia from whatever cause. The bilirubin injection test is employed only in the absence of jaundice, for if the liver's power to excrete the endogenous bilirubin is depressed it is a foregone conclusion that it will show a corresponding incapacity to excrete the injected pigment. In the absence of jaundice, however, the bilirubin injection test is one of the most reliable means of estimating the degree of liver damage. Determination of the *serum phosphatase* level is one of the most sensitive tests of liver function. In hepatic damage the level is raised.

B. TESTS BASED UPON THE METABOLIC FUNCTIONS OF THE LIVER

(a) THE LEVULOSE (FRUCTOSE) TOLERANCE TEST. In this test the blood sugar curve is determined after the ingestion of from 40 to 50 grams of pure levulose dissolved in 250 cc. of water—the dose of sugar is varied according to the subject's weight. The test is

performed in the morning, that is, after a 12 hour fast. The blood sugar level is first determined before the ingestion of the sugar and every half hour for 2 hours thereafter. The liver converts levulose to glycogen, the greater quantity of sugar so converted the less pronounced will be the rise in the blood sugar. In the absence of hepatic disease the ingestion of 40 grams or so of the sugar causes a maximum rise of the blood sugar curve of 30 mg. per cent or less above the fasting level (when this is between 80 to 100 mg. per 100 cc.); the curve returns to within 15 mg. per cent of the fasting level within 2 hours. Definite hepatic injury is indicated by a rise in the blood sugar of over 30 mg. per cent when the fasting level is between 80 and 100 mg. per cent, and a rise of 35 mg. per cent, and of 40 mg. per cent when the fasting levels are from 70 to 80 and from 60 to 70 mg. per cent, respectively. Failure of the curve to return to within 15 mg. per cent of the fasting level after 2 hours, regardless of the height of the curve, is also definitely abnormal.

(b) **THE GALACTOSE TOLERANCE TEST** (see p. 465).

The levulose and galactose tolerance tests are of especial value in that they are applicable in the presence of jaundice.

(c) Tests based upon the function of the liver to deaminate the amino-acids with the production of

urea (p. 546) or upon its detoxicating function have also been devised. Though in the dog hippuric acid is synthesized only in the kidney, in the rabbit and in man this function is performed by the liver as well. In carrying out this test benzoic acid (5.9 grams) is given orally and the quantity of hippuric acid excreted in the urine at hourly intervals for four hours thereafter is determined. If the liver possesses some reserve function 3 to 3.5 grams are excreted within this time. The determination of the *prothrombin time* (p. 91) is also employed as a liver function test. In damage of the liver, the prothrombin time is prolonged.

It is to be remembered that the foregoing are purely functional tests and that a negative result does not necessarily indicate the absence of liver injury. On the contrary, liver disease may exist without its condition being revealed by any of these means. This is obvious from the observations of McMaster and Rous and Mann and his associates upon the reserve function of the liver. The first mentioned observers showed that in the dog 95 per cent of the excretory function could be abolished before jaundice appeared; Mann and his associates found that the liver tissue of the dog could be reduced by 80 per cent or more without a fall in urea production occurring.

CHAPTER XLII

THE GALL-BLADDER AND BILE DUCTS

Anatomy

The human gall-bladder has a capacity of about 50 c. Its wall is composed of a thin layer of muscle fibers and fibro-elastic tissue. It is lined by mucosa. The muscle fibers are sparse and loosely interlaced with one another and with the strands of fibro-elastic tissue. The mucosa is surmounted by a layer of columnar epithelium.

The *cystic duct* through which the bile enters and later leaves the viscus is tortuous, kinked or S-shaped and shows spiral folds of mucosa—the *valves of Heister*—within its lumen. The functions of these folds have not been clearly defined. They are not capable, apparently, of preventing either the entrance or egress of bile into or from the vesicle, though they offer a resistance of about 25 mm. of H₂O to the passage of fluid in either direction. They possibly serve a useful purpose in preventing kinking or twisting of the viscus, and retarding the inflow of bile. They are sometimes complete or may be absent. The cystic duct joins the hepatic duct at an acute angle to form the common bile duct.

The *common bile duct* passes very obliquely through the muscular wall of the duodenum and joins with the pancreatic duct to form the *ampulla of Vater* (fig. 198). The latter opens into the duodenum through an orifice situated at the summit of a small papilla about 3½ inches below the pylorus. The ampulla of Vater is surrounded near its outlet into the duodenum by a ring of muscle fibers—the *sphincter of Oddi*. The duodenal muscle in which the oblique intramural portion of the duct is embedded, exerts when contracted, a strong pressure upon the entire length of this section of the duct. The mucosa of the common duct is devoid of the usual mucous glands, but contains special branched tubular glands lined with tall columnar cells. These glands furnish a thin fluid which dilutes the bile.

The functions of the gall-bladder though important are not indispensable since it can be removed with impunity. After such an operation, however, the larger bile ducts undergo dilatation, which may in part compensate for the removal of the viscus. The gall-bladder is absent in some animals whose habits and digestive processes are not essentially different, apparently, from those of animals which possess one. It is absent in the horse, deer and rat but present in cattle, sheep, dogs, cats and mice. It is present in fish, amphibia and reptiles and birds, but is absent from mammals lower than these

CONTRACTIONS OF THE GALL-BLADDER AND COMMON BILE DUCT

The gall-bladder shows spontaneous *rhythmical contractions* which occur at the rate of from 2 to 6 per minute (in the dog), and also a *tonic contraction* which lasts for from 5 to 30 minutes or more. The rhythmical contractions (in the dog) are capable of producing a pressure change of from 250 to 300 mm. of water which is about the maximal pressure at which bile can be secreted by the liver (fig. 199). Rhythmical contractions of the common bile duct have also been demonstrated in animals.

THE FUNCTIONS OF THE GALL-BLADDER

THE CONCENTRATION AND STORAGE OF BILE—THE SECRETION OF MUCUS

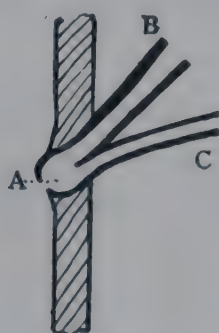
Gall-bladder bile may be some ten times more concentrated in total solids than bile collected from the hepatic duct. Water and inorganic salts are absorbed through the lymphatics and blood vessels of the gall-bladder wall. The composition of the absorbed fluid is practically that of physiological saline. Bile pigments, bile salts and cholesterol are not absorbed to any appreciable degree under normal circumstances.

It is undecided whether cholesterol is excreted by the normal gall-bladder mucosa, though Elman and Taussig present evidence for such a process. In this connection it may be mentioned that a pronounced diffuse deposition of a cholesterol ester (35 to 60 per cent of the dry weight of the gall-bladder) in the connective tissue of the human gall-bladder wall is seen as a pathological condition. The tissue of the vesicle is stiff and greatly thickened as a result of its impregnation with lipid material. The disturbances leading to this condition, which is spoken of as *cholesterosis of the gall-bladder* or, from the appearance of the mucosa, as the "*strawberry gall-bladder*," are unknown; the existence of this condition cannot, however, be used as evidence for the secretion of cholesterol by the gall-bladder mucosa under physiological conditions. (See Elman and Graham.)

To the work of Hammarsten and more recently to that of Rous and McMaster we owe the greater part of our knowledge of the absorptive powers of the gall-bladder. By means of a cannula placed in the bile duct the latter observers collected the bile as it came from the liver and compared its composition with that in the gall-bladder. The bilirubin percentages of the respective fluids were used as a measure of the degree of concentration that had been effected in the bile during its stay in the gall-bladder. The bladder bile was found to be darker, thicker and more "syrupy" than the bile collected from the ducts. It contained from 3.1 to 10.8 times more bilirubin than the liver bile. Absorption occurred with remarkable rapidity in some instances. In one experiment about 50 cc. of bile

with a functionless gall-bladder. The "white bile" under these circumstances is furnished solely by the mucosa of the ducts. It contains no pigment, bile salts or cholesterol and bears almost no resemblance to bile. The secretion of the latter has been suppressed by the rise in pressure (to 300 mm. or so of water) within the duodenal system.

If the gall-bladder is healthy and left in communication with the obstructed system the sequence of events is entirely different. Biliary stasis then causes this *greenish bile* to collect in the ducts and bladder as result of the latter's concentrating activity, and of the mucinous material which it secretes. After a lapse of weeks the imprisoned bile develops an almost tar-like consistency. The functions of the ducts and of the bladder are therefore antagonistic, the former tending



D.W

FIG. 198

FIG. 198. Diagram showing the opening of bile and pancreatic ducts into the duodenum. A, ampulla of Vater; B, bile duct; C, pancreatic duct; D.W., duodenal wall.



FIG. 199

FIG. 199. Examples of normal gall bladder contractions. Time marker, 1 second. (After Taylor and Wilson)

which entered the gall-bladder was reduced to less than 5 cc. in about 22 hours. In experiments involving the drainage of the gall-bladder through a cannula inserted into its fundus it has been shown that the mere passage of bile through the organ causes a nearly fivefold concentration. Inflammation of the gall-bladder reduces or abolishes its concentrating power.

The gall-bladder mucosa also adds to the viscosity of the bile by the *secretion* of a thick mucinous material. Little or none of this material is furnished by the bile ducts. Nor were the latter observed to have any concentrating power but were found, on the contrary, to dilute the bile with a thin watery fluid.

When the ducts were obstructed by ligation and the gall-bladder tied off, after some days a clear colorless fluid was found to have collected within the former. This fluid—the so-called "*white bile*"—is not uncommonly seen during an operation upon an obstructed bile duct associated

to dilute, the latter to concentrate the biliary fluid. The diluting effect is at first overbalanced by the concentrating action of the gall-bladder, and when the latter remains in communication with the duct system, the net result is marked thickening of the bile. There is, however, a tendency with time for the activity of the ducts to overcome that of the gall-bladder. The biliary constituents disappear and ultimately the contents of the system are entirely replaced by the thin simple secretion of the ducts and mucinous material from the bladder (hydrops). (Rous and McMaster)

These facts have a bearing upon the formation of gallstones (see also p. 468); since stasis and concentration of the bile are believed to be factors in this process it is evident that calculi are not likely to form as a result of obstruction of the *hepatic* ducts. The gall-bladder would in that case be situated beyond the obstructed system and could not exert its concentrating power.

Another type of "white bile" is sometimes produced. In dogs a clear colorless fluid is secreted by the liver cells when their true secretion is suppressed by some severe liver injury such as that induced by the administration of chloroform (Drury and Rous). "White

of this type is sometimes seen in the human subject as a result of hepatic disease.

Other functions of the gall-bladder subsidiary to its concentrating power are the *reduction in alkalinity* of the bile (p. 468) and the *equalization of pressure* within the biliary duct system. Without the ability to absorb fluid and reduce the bulk of the bile its power to equalize pressure would be negligible. It is to be remembered that the amount of bile secreted in 24 hours is one twenty times or so greater than could be contained in the gall-bladder. The loss of its function in equalizing the pressure within the duct system is probably a factor leading to the dilatation of the bile ducts, which so frequently follows removal of the gall-bladder (cholecystectomy). After this operation the flow of bile into the intestine is at first nearly continuous, but later the adaptation of the ducts permits intermittent discharge.

The importance of the gall-bladder in the control of pressure within the biliary ducts is apparent from the results of the experiments of Mann and Bollman. They found that after ligation of the common duct in dogs a rise in the bilirubin concentration of the blood did not occur until from 24 to 36 hours had elapsed, and jaundice did not appear for 2 days. If, on the other hand, the gall-bladder was removed at the time that the jaundice was fully developed within 24 hours due, presumably, to the rise in duct pressure, and the suppression of secretion of bile by the liver cells.

In dogs, cholecystectomy causes some impairment of liver function, as shown by the serum phosphatase test, (p. 469) for at least 70 days following the operation. In man, the excretion of urobilinogen is reduced for a short time after this operation.

THE FILLING AND EVACUATION OF THE GALL-BLADDER

As the bile as it leaves the liver flows into the biliary duct and thence into the common bile duct. During fasting its entrance into the duodenum is blocked by the sphincter of Oddi which remains tonically contracted. As the bile accumulates within the duct its pressure rises, reaching a height of from 50 to 70 mm. of water. This pressure forces its way along the cystic duct into the gall-bladder. During fasting therefore the gall-bladder becomes gradually distended with retained bile.

The nature of the force by which the gall-bladder is evacuated has been a question of some debate. The wall of the gall-bladder is so thin, and its muscle fibers so sparse, that it seemed unlikely that it could exert the pressure required to discharge its contents—especially since the gall-bladder is evacuated with considerable difficulty by manual compression. Intra-abdominal pressure, “milking” action exerted by the duodenal movements, and simple leaking into the duodenum as a result of relaxation of the sphincter of Oddi have been variously suggested as possible factors. Some have even contended that bile does not leave the gall-bladder by the cystic duct but is completely absorbed (Sweet). It has however, been proved quite definitely as a result of evidence derived from several modes of investigation that the contractions of the gall-bladder wall itself are responsible for the expulsion of its contents. The times of emptying of the gall-bladder are related to gastric digestion. During fasting it remains distended with bile though the sphincter guarding the common duct is relaxed, plainly indicating that the viscus is competent to retain the bile without the aid of the sphincter of Oddi. That changes in intra-abdominal pressure are not responsible for its emptying was shown by Mann and Higgins working with guinea-pigs. The gall-bladder of this species can be readily mobilized.

The abdomen was opened under local anesthesia, the gall-bladder exposed and drawn outside the abdominal wound, which was then sutured around the cystic duct. The vesicle was observed to contract and expel its contents in response to food placed in the duodenum. It was also shown that in fish, which of course have no diaphragm and in which, apparently, the intra-abdominal pressure remains constant, intermittent evacuations occurred. In dogs the influence of the sphincter was removed by suturing a catheter into the common duct; the abdomen was left open in order to minimize the effects of intra-abdominal pressure. The gall-bladder remained distended and expelled its contents only during the digestion of a meal.

When the walls of the gall-bladder contract, bile is discharged along the cystic and common ducts into the duodenum. The sphincter of Oddi normally can withstand a pressure of 100 to 120 mm. of water but the pressure developed by the contractions of the gall-bladder in dogs was shown by Mann and his associates to amount to over 250 mm. H₂O. It is probable moreover that relaxation of the sphincter occurs as part of a coordinated mechanism when the bladder wall

contracts, and that the passage of bile through the sphincter is not simply a matter of the latter "giving way" before the biliary pressure created by the gall-bladder contractions. The duodenal muscle surrounding the oblique intramural portion of the common bile duct (p. 471) is capable when contracted of offering a resistance of over 750 mm. of water. Since this is much higher than the pressure which contractions of the gall-bladder can exert, the flow of bile is completely blocked during contractions of the duodenal muscle but during the latter's relaxation the pressure is relieved (fig. 200). Therefore, during the evacuation of the gall-bladder and active duodenal movements, the bile may be observed to enter the duodenum in squirts. This is not due to the "milking" action of the peristaltic movements of the bowel but is simply the result of the alternate blockage and release of the duct, the bowel

gall-bladder when rendered opaque to the X by the administration of tetraiodophenolphth (p. 475) can also be seen to discharge its contents in response to a meal of fat. Its contractions during operations have also been observed frequently. The products of fat digestion, hydrochloric acid of a strength comparable to that in the chyme, or magnesium sulphate if placed in the duodenum, cause evacuation of the gall-bladder and relaxation of the sphincter of Oddi. Bile salts injected intravenously on the other hand, cause relaxation of the gall-bladder. Liquid petrolatum introduced into the duodenum is without effect.

The mechanisms controlling evacuation of the gall-bladder

(a) NERVOUS. It has been mentioned that relaxation of the sphincter of Oddi prob-

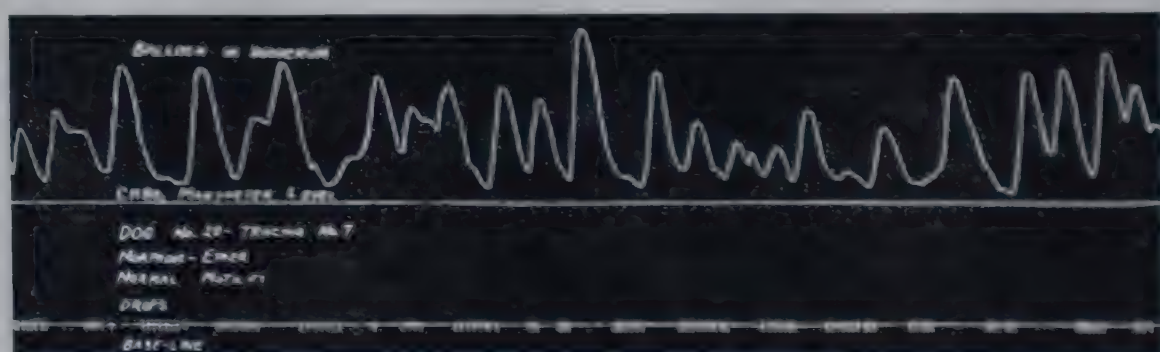


FIG. 200. This figure shows the relation between duodenal contractions and flow of bile (indicated in the near bottom of figure) from the common duct into the duodenum. (After Lueth.)

movements being incapable of causing any flow of bile when the gall-bladder is not contracting.

The most effective stimulus for the discharge of bile is fatty food, particularly egg-yolk, cream or olive oil. It appears that some degree of digestion of the fat must occur before evacuation results. The effect of fat upon the gall-bladder was shown definitely by Boyden. He found that during a period of fasting the gall-bladder in the cat was distended with bile, and its walls so stretched that they were reduced to about one-fifteenth of their thickness in the collapsed state. It emptied slowly after a meal, being collapsed, or nearly so, in from 1½ to 2 hours. The effect of meat upon the discharge of bile is much less than that of fat. Pure protein, such as egg white, and carbohydrate food is almost without effect. These findings have been amply confirmed by several observers. Whitaker and his associates, for example, observed changes in the contour of the gall-bladder after filling it with iodized oil and examining it radioscopically. The human

occurs as the gall-bladder contracts. An uncoordinated action of this nature points to a nervous mechanism. The latter may depend upon the intrinsic nervous plexuses in the walls of the biliary structures. The gall-bladder contractions initiated by the stimulus of a meal might be similar to short reflexes through the intrinsic plexuses of the stomach or duodenum and biliary tract. Nervous mechanisms are also indicated by the following observations. Electrical stimulation of the stomach and duodenum are sometimes followed by contractions of the gall-bladder. Contractions are occasionally induced by psychological influences, e.g., the smell or taste of food. The gall-bladder also responds to experimental excitation of the vagus or sympathetic nerves. Experiments attempting to demonstrate the precise actions of the extrinsic nerves upon the gall-bladder movements have, however, given conflicting evidence. Several observers have obtained weak motor effects from both vagus and sympathetic stimulation, a motor action

the latter is also indicated by the fact that adrenaline is excitatory.

The results of the experiments of Johnson and his associates, however, seem clear cut. Section of the right vagus nerve of the cat retarded emptying of the gall-bladder as a result, apparently, of the interruption of motor fibers to the gall-bladder and of inhibitory fibers to the sphincter of Oddi. The left vagus was found to carry motor fibers to the gall-bladder, but apparently does not contain inhibitory fibers to the sphincter. Reflex effects upon the movements of the gall-bladder may be initiated from other abdominal viscera. Stimulation of the duodenum, for example, causes inhibition of the movements of the gall-bladder. This reflex is abolished after section of the splanchnic nerves and excision of the celiac ganglion.

HORMONAL. Nevertheless, nervous mechanisms are not essential to gall-bladder activity; this is evident from the fact that the reaction to introduction of fat into the duodenum occurs without all nervous connections between the biliary and gastro-intestinal tracts, and between the brain and the central nervous system have been severed. That gall-bladder contractions can occur under such circumstances suggests, of course, a humoral or hormonal mechanism. Boyden found that the blood of an animal taken at the height of digestion, when injected into a fasting animal, causes the evacuation of bile; blood from a starved animal has no such effect.

Boyden obtained an acid extract from the mucosa of the upper part of the intestine which caused contraction of the gall-bladder when injected intravenously into animals. Acid itself is without effect when injected. Nor will fat or its derivatives excite contractions of the gall-bladder when administered intravenously. Acid and other substances which are excitatory when placed in the duodenum or fed therefore act apparently by stimulating the production or liberation of a hormone from the intestinal mucosa. The active principle is related to secretin but not identical with this hormone, for it does not cause pancreatic secretion, and secretin does not cause gall-bladder contractions. In crossed circulation experiments introduction of acid into the duodenum of one animal caused contractions of the gall-bladder in the other. Ivy and Oldberg named this principle "*cholecystokinine*." As little as 0.2 mg. of solid material prepared from a potent extract causes definite contractions of the gall-bladder. It is free from histamine and other

vasodilator substances. Its effect has been demonstrated upon man. The transfusion of blood from a human subject digesting egg yolk has been found to cause evacuation of the gall-bladder of the recipient. No effect was observed with blood from a fasting donor.

The actions of drugs upon the motility of the gall-bladder. Adrenaline, pitressin, histamine and mecholyl stimulate the smooth muscle of the gall-bladder, whereas morphine, ergotamine and atropine are inhibitory.

CHOLECYSTOGRAPHY

Graham and Cole showed in 1924 that if the chlorine radical of a dye such as tetrachlorophenolphthalein, which is excreted selectively by the liver, be replaced by iodine or bromine, the compound, after concentration in the gall-bladder, is opaque to the X-rays. Sodium tetra-iodophenolphthalein or the corresponding bromine compound (sodium tetra-bromphenolphthalein) is given intravenously or by mouth in a special coated capsule. After fasting for a period of about 14 hours a radiogram is taken. The normal gall-bladder at this time shows a well defined shadow. The gall-bladder is then stimulated to contract by means of a meal containing egg yolk and cream, and a second radiogram taken 5 hours later, when the normal organ should be found practically empty. The depth of the shadow after dye administration depends directly upon the concentrating power of the gall-bladder. For this reason a diseased gall-bladder may throw only a faint shadow or none at all.

Gallstones, which are relatively transparent to the X-rays, especially those of a high cholesterol content, show up against the gall-bladder shadow. Gallstones containing more than 0.5 per cent of calcium are visible without the aid of an opaque dye.

AFFECTIONS OF THE GALL-BLADDER AND BILE DUCTS

Among the common diseases of the gall-bladder are *inflammation* (*cholecystitis*), *gallstones* (*cholelithiasis*) and *new growths*. The factors involved in the formation of gallstones have been considered (p. 467).

In the absence of inflammation, stones in the gall-bladder give rise, as a rule, to no definite symptoms, but in their passage along the ducts severe pain—*biliary colic*—may be experienced as a result of the spasmodic contractions of the gall-bladder and consequent distension of the duct walls. Vomiting may occur as a reflex phenomenon. In the dog pain is produced when the gall-bladder is distended by a pressure of 540 mm. of water. This, of course, is a much higher pressure than the contractions of the gall-bladder can create. Pain is produced, however, by

distending the *ducts* with a pressure of 270 mm. of water—just about the maximal pressure which the gall-bladder contractions can produce. The cause of the expulsion of the stone from the gall-bladder is not altogether clear. Though contractions of the gall-bladder have been observed to cause movements of stones within its cavity, and even to force a stone into the cystic duct, gall-bladder contractions do not in the majority of instances offer satisfactory explanation for the expulsion of the stone. According to some, inflammation and distension of the gall-bladder are important factors leading to the passage of the stone into the cystic duct.

Biliary dyskinesia

It is now generally recognized that biliary colic may occur in the absence of stone, inflammation or of any anatomical abnormality, such as kinking of the cystic duct, which would hinder the expulsion of bile from gall-bladder. In such instances the colic has a functional origin, being due to the gall-bladder contracting

against a sphincter of Oddi in a state of spasm. Normally as already mentioned the sphincter relaxes and the gall-bladder contracts. In biliary dyskinesia nervous mechanisms upon which this reciprocal action depends are, apparently, disordered. It has also been claimed that a sphincter exists at the junction of cystic duct with the gall-bladder and that spasm of this ring of muscle during contraction of the gall-bladder may give rise to biliary colic.

Gall-bladder disease frequently gives rise to disturbances of other organs, particularly of the stomach. Anacidity or hypoacidity and increased motility of the pyloric part of the stomach are commonly encountered. Ivy and Fishback experimenting with dogs found that mild stimulation of the biliary tract inhibited gastric motility and lowered gastric tone. They suggest that in the human subject stimulation of this nature is conducive to gastric flatulence and belching. A sudden sharp distension of the bile duct caused pylorospasm and vomiting in their animals. According to some authorities dyspeptic symptoms in from 40 to 50 per cent of subjects are due to biliary tract disease. Cardiac irregularities may result through reflexes initiated from the gall-bladder or bile ducts (p. 209).

CHAPTER XLIII

THE MOVEMENTS OF THE ALIMENTARY CANAL

THE PHYSIOLOGICAL PROPERTIES OF SMOOTH (PLAIN, INVOLUNTARY OR NON- STRIATED) MUSCLE

The chief features of smooth muscle whereby it differs from skeletal muscle are: (a) sluggishness of contraction; (b) greater extensibility; (c) the exhibition of sustained contraction or tonus, even when isolated from the central nervous system; (d) the power of rhythmical contraction; (e) the possession of a double autonomic innervation (sympathetic and parasympathetic); (f) greater sensitivity to thermal and chemical influences and to certain types of mechanical stimulation, e.g., stretching, but a lower excitability to electrical stimulation; and (g) longer chronaxie.

As in the case of skeletal muscle and of heart muscle (p. 216), the force of the contraction of smooth muscle is dependent, within physiological limits, upon its initial length. Thus distension of the wall of the intestine as by the presence of gas or of fluids secreted as a result of a saline cathartic, causes powerful contractions of the bowel wall.

Tonus of smooth muscle is defined by Evans as the resistance which its substance offers to extension. The degree of tonus (T) may therefore be expressed thus;—

$$T = F/L$$

where F is the extending force and L the final length of the muscle subjected to the extending force.

The rhythmical contractions of smooth muscle are superimposed upon the tonus state which varies independently of the rhythmical contractions themselves and may be of high, of medium or of low degree. The processes underlying the production of tonus in smooth muscle are not clearly understood though it is possible that they are not fundamentally different from those responsible for the rhythmical contractions. It is probable that, as in skeletal muscle (p. 786), only a proportion of the fibers are contracting at one time during the tonus state. That is, at groups of fibers contract in rotation.

The chemical changes accompanying the contraction of smooth muscle are probably similar

to those occurring during the contraction of skeletal muscle (p. 612). Glycogen is broken down and lactic acid produced. In the absence of oxygen, lactic acid accumulates in the muscle contracting in nitrogen, and disappears upon the admission of oxygen.

The tonic contraction of smooth muscle is associated with a negligible expenditure of energy. The tonus mechanism is relatively insusceptible to fatigue; heat production and electrical changes are not detectable; and a rise or a fall in the degree of tonus is not accompanied by a corresponding change in oxygen consumption. Evans found, in fact, that a muscle, when in high tonus, used slightly less oxygen than when relaxed. The tonus of the smooth muscle of the gastro-intestinal tract is dependent mainly upon the intrinsic plexuses, though it is influenced through the extrinsic nerves as well. Tonus changes are also brought about through influences, e.g., changes in hydrogen ion concentration, acting directly upon the muscle fibers.

Postural tone

When a hollow viscus such as the stomach is gradually distended its walls become accommodated automatically to the greater volume, though the tone of the muscle at the new length is altered little from that existing before the distending force was applied. The pressure within the bladder or within the stomach (p. 487), for example, does not increase, or does so very temporarily when the contents of these viscera are increased in volume several fold. The tone of the muscular walls becomes adjusted to the "posture" of the viscus; the adjustment is analogous to the lengthening and shortening reactions of skeletal muscle (p. 827).

The inner mechanism whereby this "postural tone" is brought about is obscure. The great increase in capacity which can occur in a viscus such as the stomach is difficult to explain simply by assuming what the individual muscle fibers are increased in length. It has been suggested, therefore, that the muscle fibers, which are disposed in layers in the walls of the hollow viscera, slip over one another, the wall thus becoming

increased in area but reduced in thickness (Grützmacher).

MASTICATION

This act comprises movements of the lower jaw, lips, tongue and cheeks. Tearing of the food is effected mainly by the incisor teeth, grinding by the molars. The jaw movements consist of elevation and depression, protrusion and retraction, together with side to side motions; they are all controlled through the inferior maxillary division of the trigeminal nerve; they result in the conversion of the food into a fine state of division and its thorough moistening with saliva. The movements of the tongue and cheeks serve to pass fresh food material between the teeth, and to collect it after treatment by the teeth into a bolus suitable for swallowing.

THE ACT OF SWALLOWING (DEGLUTITION)

It has been customary since the time of Magendie to divide the act of swallowing into three stages.

The first stage is under voluntary control. The food which has been transformed into a soft mass by the act of mastication is brought into position upon the dorsum of the tongue, and by the action of the lingual muscles is rolled backwards towards the base of the tongue, where it lies just in front of the isthmus of the fauces. The *mylohyoid* muscle (p. 474) then contracts, pressing the tongue against the hard palate and carrying its base, which is also rotated through the arc of a circle having the hyoid bone as its center, sharply backwards. This movement which is effected with great speed propels the bolus with considerable force into the pharynx where it enters upon the second stage of its journey to the stomach. Other muscles, the *hyoglossi*, the *glossopalatini* and the *styloglossi* acting in conjunction with the *mylohyoids* assist in drawing the tongue backwards. As a result of the muscular movements, chiefly in the *mylohyoids*, a pressure of 20 cm. of water is developed in the posterior part of the mouth, pharynx and upper part of the esophagus. A negative pressure, however, exists in the anterior part of the mouth. A negative pressure also normally exists in the closed mouth at other times, which aids in holding the lower jaw in the elevated position.

The second stage is brief and is occupied in guiding the food through the pharynx and past the openings that lead from it. The muscular

movements during this stage are pure in nature. Having once passed through the isthmus of the fauces, the further progress of food is beyond voluntary control; though sometimes material can be returned to the mouth by a special effort of coughing or "clearing the throat." Upon the food entering the pharynx the constrictor muscles contract; the tongue is thus brought to bear upon the food forcing it into the esophagus, the *palatopharyngeus* and *pharyngeus* muscles at the same time draw the pharynx upwards over the bolus. There are, however, three other possible paths or directions along which the food may travel: (a) forward again into the mouth, (b) upwards through the naso-pharynx, and (c) downwards into the larynx. The return of food into the mouth is prevented by the contraction of those muscles which force the pharynx during the first stage. The



FIG. 201. Typical graphs of pressure in the pharynx during swallowing. Upper tracing (white), pressure in larynx recorded on a tambour. Lower tracing (black), record of pharyngeal pressure. (From after Anrep.)

of the tongue remains elevated and drawn upwards while the *pharyngeopalatini* and *glossopalatini* forming the faucial pillars contract, approximating the latter structures toward the midline, narrow the opening into the nasopharynx. A negative pressure amounting to 35 cm. of water is created in the pharynx and esophagus during this stage (fig. 201) thus aiding in the descent of the bolus.

The opening into the naso-pharynx is closed by the contraction of the *levator veli palatini* and *uvulae* muscles which pull the soft palate so that its posterior edge is approximated to the posterior pharyngeal wall. When this movement cannot be accomplished as in post-diphtheritic paralysis, bulbar palsy, etc., attempts to swallow liquids are followed by their regurgitation into the nasal cavities.

The entrance of food into the larynx is prevented by the contraction of the *epiglottis* muscle which raises the organ, bringing it under the shelter of the epiglottis and the tip of the tongue. The epiglottis itself, by

essential for the protection of the laryngeal opening, since when it is destroyed there is little fault in preventing the food from entering the air passages—the elevation of the larynx is the important safeguard; when it is fixed by base swallowing is difficult or impossible.

The epiglottis was at one time thought to serve as a sloping lid for the larynx over which the food passed in its passage downwards. This structure, however, stands erect and the food passes over its dorsal (posterior) not over its ventral surface. Coincidentally with the upward movement of the larynx the vocal cords are approximated. This is effected by the contraction of muscles attached to the arytenoid cartilages which are thereby drawn forwards from their usual positions against the posterior pharyngeal wall, and rotated medially. This manoeuvre has the two-fold effect of closing the glottis and causing the upper opening of the esophagus to gape. The food, being subjected to pressure by the contraction of the laryngeal constrictors, is forced along the path of least resistance.

At the short inspiration (inspiration of swallowing) which occurs at the very commencement of the first stage, and is followed by complete inhibition of expiration which persists until the end of the second stage.

The third stage involves the passage of the food into the esophagus. The food is seized by a peristaltic wave (p. 496) which, travelling along the esophagus, carries the material before it into the stomach. The cardiac sphincter guarding the lower end of the esophagus and which at other times is kept tonically closed relaxes upon the arrival of each of the bolus which is then swept into the stomach by the wave of constriction which follows.

Relationships. The food reaches the upper end of the esophagus in about 1 second after the commencement of the swallowing act. The rate of progress of the bolus along the human esophagus is not the same at all levels. The muscle in the upper or cervical portion of the tube, which is about 6 cm. long is of the striated type and consequently is capable of rapid contraction. Solid food traverses this section in about 1 second.¹ In the upper thoracic portion, which is approximately 10 cm. in length, the fibers are mixed, being striated, others unstriated, and the food takes 1.5–2.0 seconds to pass. In its lower thoracic portion the tube is composed entirely of unstriated muscle. Its length has not been determined precisely but the

esophagus of the dog is composed of striated muscle throughout.

Food takes about 3 seconds to pass through it. Solid or semi-solid food therefore takes between 6 and 7 seconds to pass from the mouth into the stomach.

When liquids are drunk the swallowing process is not quite the same. During the first stage the liquid is squirted forcibly into the pharynx and down the esophagus by the contraction of the mylohyoid and in less than a second reaches the lower end of the gullet which becomes relaxed throughout its entire length. That the fluid is not carried by a peristaltic wave but passes down the esophagus with great rapidity can be demonstrated by means of X-ray or by auscultation over the lower part of the esophagus when the sound of the fluid arriving here can be heard. On this account the accidental drinking of corrosive liquids tends to cause injury not equally throughout the length of the esophageal mucosa, as would occur if it were carried by a peristaltic wave, but more especially at certain points where the fluid strikes or collects, e.g. in the upper part of the esophagus and above the cardia. When a single mouthful of liquid is drunk the cardiac sphincter does not relax immediately upon the arrival of the fluid. This collects above the sphincter until a peristaltic wave, started in the upper part of the esophagus, arrives a few seconds later to relax the sphincter and carry the accumulated fluid through it. In other instances, the fluid is not shot down the full length of the tube but only as far as the lower part of the cervical segment or into the thoracic portion. The distance depends upon the degree of relaxation of the muscular walls and the force of the propulsive movement. When a series of mouthfuls of liquid are swallowed in rapid succession, as in drinking a glass of water, the esophagus usually relaxes throughout its length, and the fluid is projected to its lower end or even through a relaxed cardia directly into the stomach.

The first stage for the swallowing of liquids is not the same for all species. In the dog and most other mammals the squirting action is important. On this account these animals can drink in the head down position and force the fluid into the esophagus against gravity. This ability is dependent upon the contraction of the mylohyoid aided by the negative pressure in the pharynx and esophagus; removal of the pharyngeal constrictors does not interfere with it. In birds such as fowl, geese, etc. as was shown by Cannon and Moser, the passage of liquids as well as of solids is dependent upon peristalsis; there is no squirting action. These animals in consequence must raise the head in order to swallow liquids which are thus allowed to trickle by gravity into the esophagus. If the mylohyoid muscle is denervated in the dog liquids must be swallowed in a similar manner.

THE INNERVATION OF THE SWALLOWING REFLEX

Upon first thought, it might appear that the swallowing act could be initiated when desired, yet it is only the first stage that is under voluntary

control. If one wishes to swallow when the mouth is free of food or foreign material, a little saliva is passed backwards by the tongue and thus serves as a mechanical stimulus for the initiation of the second and third phases of the act which are purely reflex. If the mouth is kept perfectly free of saliva deglutition becomes impossible. The afferent fibers of the reflex are furnished by the *hypoglossal* nerve to the lingual muscles; the third division of the *trigeminal* nerve to the mylohyoid; the pharyngeal branches of the *glossopharyngeal* nerve and the pharyngeal and esophageal branches of the *vagus* (fibers of accessory nerve, see p. 862) to the muscles of the pharynx and esophagus.

That the carriage of food along the upper two-thirds or so of the gullet is dependent upon extrinsic nerves, and that the peristaltic contraction is not initiated or controlled by nerve plexuses within the wall of the tube, nor yet the result of a property inherent in the muscle itself was shown by the following experiment of Mosso. When the esophagus was cut across and a swallowing reflex then elicited by stimulating the pharynx, the peristaltic wave which followed "crossed" the gap and appeared in the lower segment. If the *vagus* fibers going to the esophagus are divided, paralysis with complete relaxation and dilatation of the upper two-thirds of the tube results; no peristaltic wave can be evoked, and food does not enter the stomach. On the other hand, the lower quarter or third, in an animal such as the cat of which this portion of the gullet is composed of unstriped muscle, continues to show active peristalsis and may for a time enter into a state of spasm. The cardiac sphincter (p. 481) passes into a state of tonic contraction. Stimulation of the *vagus* causes, as a rule, a strong contraction of the entire esophagus. The sympathetic causes, according to Knight, contraction of the upper and middle thirds and inhibition of the lower third of the tube.

The foregoing experimental results may be taken as evidence that peristalsis in the upper portions of the esophagus is carried out through a central reflex. In the lower esophagus, which in many animals and in man is composed of unstriped muscle, the initiation and transmission of the wave, like similar movements of the intestine (p. 496) devolves upon the intrinsic nervous mechanism. But also like the intestine this part of the tube can be influenced through the extrinsic nerves.

The afferent fibers of the reflex are furnished by the pharyngeal branches of the *trigeminal*, *glossopharyngeal*

nerve and the pharyngeal and superior laryngeal branches of the *vagus*, innervating the regions about the entrance to the pharynx. Usually a certain fairly well defined area of the fauces, the palate or of the pharyngeal wall—the location depending upon the particular animal species—can be stimulated which is more sensitive for the eliciting the reflex than any other. In man and cat, for instance, the most sensitive is the mucosa of the posterior pharynx supplied by the *glossopharyngeal*; in the dog it lies in the region of the tonsil and palate, the sensory innervation of the latter chiefly through the *trigeminal*. The *vagus* is also the most sensitive region in the larynx, though stimulation of other areas, such as the entrance to the larynx or the base of the tongue will also elicit the reflex. In man, the sensitive area has not been precisely determined, but the reflex is readily induced by stimulation of the posterior pharyngeal wall or of the base of the tongue. If the impulses from these areas be annulled by excision, swallowing is most difficult or even impossible. The central reflex cannot be initiated in the esophagus itself; a bolus placed in its middle third remains in position until the reflex is evoked by stimulating the pharyngeal wall.

Experimental stimulation of the central end of the superior laryngeal nerve will elicit the complete set of swallowing movements. The *glossopharyngeal* nerve contains afferent fibers which excite the reflex, others which inhibit it. A reflex started by stimulation, say, of the superior laryngeal may be cut short by stimulation of the central end of the *glossopharyngeal*. The tonic inhibitory effect of the *glossopharyngeal* may be shown by simply cutting the nerve, when the esophagus passes into a state of tonic contraction which persists for some time. The afferent *glossopharyngeal* fibers responsible for the inhibitory effect respond to a milder stimulus than those which excite the reflex. The *glossopharyngeal* also contains those fibers through which the reflex of respiration is effected reflexly during the act of swallowing the food through the pharynx. Stimulation of the central end of the nerve causes the breath to be immediately checked, either in inspiration or expiration according to the phase during which the stimulus is applied. The inhibitory effect of deglutition upon respiration may be demonstrated when the breath is held until the desire to breathe is imperative the distress is momentarily relieved by swallowing.

Deglutition centers

A large number of different nerves involved in the act of swallowing and the smooth manner in which the act, once initiated, is carried to completion indicate that the cranial nuclei are woven together by association fibers into a coordinated mechanism in which each nuclear part of the mechanism coming into action in accurately timed sequence and only, when the first of the series is excited. The central nervous tissue comprising this central mechanism is therefore diffuse and extends throughout the pons and medulla. A circumscribed area or center apparently does not govern this complicated mechanism. Marked this area to lie in the neighborhood of the nucleus ambiguus and above but independent of the respiratory center. Here, it is presumed, the afferent impulses are received and relayed to the motor nuclei. In progressive bulbar palsy the central mechanisms are very gravely affected as a result of the successive involvement of several nuclei.

PERISTALSIS IN THE ESOPHAGUS; HEART BURN; BELCHING

According to Alvarez, reverse wavelets or peristalsis commencing at the cardia and passing down along the esophagus to the pharynx is an uncommon occurrence in man; but reverse peristalsis is not seen unless some lesion exists. The reverse ripples in the esophagus are thought to be responsible for some symptoms of dyspepsia, e.g., the deposition of food upon the back of the tongue, bad breath, regurgitation of fluids into the mouth. Evidence of the existence of reverse movements in the esophagus was obtained by Kast who found lycopodium spores swallowed in a capsule recoverable from the mouth washings next morning in over 50 per cent of a series of human beings. The possibility of material from even the small bowel reaching the mouth is strongly suggested by the fact that lycopodium spores introduced into the colon by enema have been recovered some hours later from washings of the mouth.

"Heart Burn" is ascribed by Alvarez to the irritation of the mucosa of the upper part of the esophagus by acid fluid regurgitated from the stomach. Payne and Periton suggest that a tonic contraction of the esophagus set up by the acid stimulus is responsible for the sensation. Jones and others have produced it in normal persons by

distension of the lower third of the esophagus. The introduction of acid, cold water or gastric contents into this part of the esophagus also caused the burning sensation. Specimens of the wall of the tube was observed at the level in contact with the material and reversed peristalsis above. It is generally agreed that the sensation does not originate within the stomach itself.

BELCHING. The tendency, after a meal, for small amounts of gas to be expelled from the stomach into the esophagus and mouth is experienced by most normal persons. It is brought about, according to Alvarez, by reverse waves originating in the cardiac region of the stomach and ascending the esophagus. The repeated belching of gas is, however, abnormal. The gas in these instances is not, as a rule, produced by digestive or fermentative processes in the stomach, but is simply air which has been previously swallowed (aerophagy); it has the composition of atmospheric air. The greater part of the swallowed air does not enter the stomach but is held in the lower part of the esophagus until a sufficient volume has collected to give the subject a certain satisfaction when it is belched. The condition is seen in the nervous type of subject or in one who has some gastric discomfort; he resorts to the trick in an effort to gain relief. The intragastric pressure is not increased above the normal, apparently, in subjects who have the sensation of "gas on the stomach" and the pressure is not lowered after gas has been belched.

THE CARDIA

The muscular ring encircling the lower end of the esophagus is commonly known as the cardiac sphincter, though, as a matter of fact, in man the thickness of the muscle in this situation is scarcely greater than that in the rest of the tube. We have already seen that the cardia is held tonically contracted but relaxes upon the approach of a peristaltic wave or may even remain relaxed during a series of swallows, as in drinking (p. 475).

Experiments upon animals suggest that the cardia is supplied with both motor and inhibitory fibers from the vagus; stimulation of this nerve though followed in many cases by relaxation of the sphincter, at other times causes contraction. The character of the response, inhibitory or excitatory, depends, apparently, upon the degree of tone, high or low respectively, exhibited by the sphincter at the moment of stimulation. Observations upon cardiospasm (q.v.) suggest, however, that

in the human subject at any rate, *the chief influence exerted by the vagal fibers is inhibitory.*

The cardia is also innervated by the sympathetic, but there has also been some uncertainty as to whether this nerve exerts an inhibitory or an excitatory action. As in the case of the vagus both inhibitory and motor effects have been reported (Carlson) to result from its stimulation. However, *its predominant function in the human subject is probably excitatory.* The fact that section of the vagi causes the cardiac sphincter to enter into a state of spastic contraction indicates that in animals also, the sympathetic is mainly motor and the vagus inhibitory. Confirmatory evidence for this statement has been obtained recently by Knight in experiments upon cats. Vagal stimulation was followed in all cases by relaxation of the sphincter; sympathetic stimulation invariably caused contraction.

The cardia relaxes much more readily to pressure applied to its esophageal aspect than to pressure from within the stomach. In animals, a pressure of from 5 to 7 cm. of water on its upper surface is sufficient to cause relaxation, but a pressure of 25 cm. is required to be exerted from the stomach side. Alvarez found, however, that in the human subject the mere pressure of the stomach contents upon the cardia may cause it to relax. This fact was brought out by placing persons in the head down position. The tonicity varies in degree in different individuals, and in some, simply bending over forces the cardia, and causes a reflux of fluid into the pharynx or mouth, as a result, no doubt, of the compression of the abdomen, and the consequent elevation of intragastric pressure. It is to be recalled in this regard that the pressure in the esophagus is, like that within the rest of the thorax generally, subatmospheric. In individuals in which the tone of the cardia is lessened the "negative" pressure in the esophagus together with any increase of pressure in the abdomen, will encourage the regurgitation of fluid from the stomach.

The tone of the cardia is inhibited by mild stimulation of the gastric mucosa, and by sensory impulses arising in the mouth and pharynx. Its tone increases as digestion proceeds. The factor responsible for the increased tone does not appear to be the acidity of the gastric contents; the hypertonicity apparently is a part of the general increase in tone that occurs in the fundic portion of the stomach with the progress of digestion.

The tone of the sphincter may be increased reflexly by abnormally strong stimulation of the

stomach or of more remote regions of the alimentary tract. Afferent impulses arising from diseased gall-bladder and other abdominal organs have been held responsible for abnormally hypotonic states of the cardia.

CARDIOSPASM. Cardiospasm is the term applied to a condition in which the sphincter does not relax properly during deglutition; difficulty in swallowing (dysphagia) results, the subject complaining that food "sticks in his throat." X-ray examination frequently shows that the lower portion of the esophagus is dilated into a funnel-shaped or fusiform structure. The condition is usually one of incoordination between the muscle of the esophageal wall and the sphincter—*achalasia*—rather than one of actual spasm. The mode of its production is not known for certain. In some instances it may be reflex in nature and due to the irritation of afferent fibers in the stomach, gall-bladder or other abdominal viscus. In two cases reported by Rake, in which tissue was obtained for histological examination, degeneration of Auerbach's plexus (in which the vagal fibers end) was found. This observer considers the condition analogous to Hirschsprung's disease (p. 508) which is due to an imbalance between sympathetic and parasympathetic influences. These findings suggest that the normal action of the vagus upon this part of the alimentary tract of the human subject is to raise the tone of the esophageal wall and lower that of the cardia. Increased resistance at the cardia together with dilatation of the esophageal wall would therefore naturally result from disease of the vagal endings. Knight has reported treatment of cardiospasm and achalasia by gastric sympathectomy. But this operation which was designed to remove excitatory impulses is not, as a rule, permanently successful.

MECHANICAL FACTORS IN THE PHYSIOLOGY OF THE STOMACH

GENERAL CONSIDERATIONS. SHAPE, POSITION AND DIVISIONS OF THE STOMACH

The normal position of the empty human stomach is not horizontal, as used to be thought before the development of roentgenography. The greater part of the viscus is vertical or nearly vertical. In some subjects the stomach is shaped like the letter J, in others like a steer's horn and in others again like a reversed L. The majority of normal stomachs are J-shaped. In this type the pylorus lies at a higher level than the lowest part of the greater curvature and the body of the stomach is nearly vertical. In the steer-horn and reversed L types, on the other hand, the pylorus lies on a level with or below the most dependent part of the greater curvature. The body of the reversed

L-shaped stomach is also nearly vertical whereas that of the steer-horn type slants from above downwards and to the right (fig. 202). The hypotonic or atonic stomach tends to assume the J-shape; the hypertonic stomach is of the steer-horn type. The tone of the reversed L-shaped stomach is intermediate between the two.

The lowest point of the greater curvature reaches, usually, to about the level of the umbilicus, or to a line drawn between the highest points of the iliac crests. But even in quite healthy and apparently normal individuals it is often well

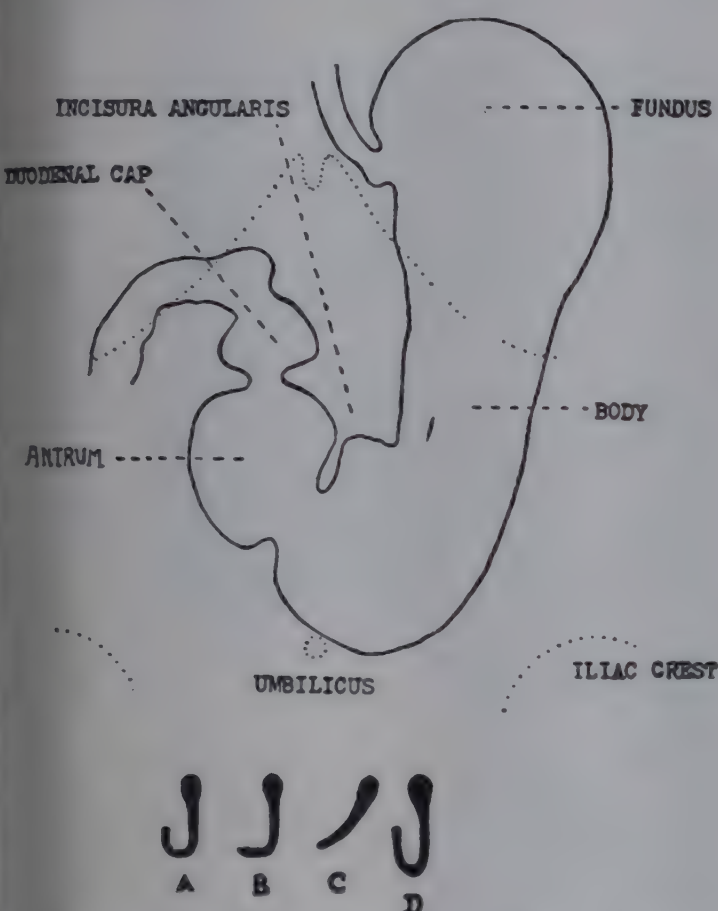


FIG. 202. Diagram showing the position and subdivisions of the stomach. A, B and C represent J, reversed L and steer horn types of stomach, respectively. D, stomach of the J-shaped type with the greater curvature lying well below the level of the umbilicus. Antrum is also known as the vestibule.

below the umbilicus in the standing position. A low position of the greater curvature has been looked upon in the past as pathological and has been believed to be the cause of various dyspeptic symptoms. X-ray examinations, however, have shown that in a large proportion of perfectly healthy persons the lower limit of the stomach may even be well down in the pelvis. But there is no "dropping" or ptosis of the viscus in the true sense, for the fundus remains in contact with the diaphragm. That is, the stomach is elongated but no downward displacement of the organ as a whole occurs. Most observers now believe that

the descent of the greater curvature is an unusual finding which, though sometimes associated with digestive disorders is not, as a rule, a cause of them, and may usually be disregarded. The stomach does not empty itself by gravity, but through the contraction of its muscular wall like any other part of the digestive tube, of which it is merely a dilated segment. It is not to be expected, therefore, that a lower position of a portion of a stomach with healthy muscle would necessarily affect its emptying any more than the evacuation of a loop of intestine would be influenced by the position which it occupied in relation to the rest of the intestinal canal. The pylorus lies in or a few centimeters to the right or left of the mid-line. When the stomach fills, the pylorus moves to the right.



FIG. 203. Upper series, X-ray appearance of stomach at 200 second intervals following the ingestion of a liquid meal. Lower series, appearance of stomach at 5, 5, 5 and 10 minute intervals, respectively, after the ingestion of a solid meal. (After Wilson, Dickson and Singleton.)

The wall of the stomach is composed of a serous coat and three layers of muscle fibers—longitudinal, circular and oblique, from without inwards. The mucous membrane is thrown into numerous ridges or folds called *rugae*. These are particularly well marked when the stomach is empty but tend to become flattened out as the organ becomes distended. There is a well marked *muscularis mucosae*. The capacity of the stomach is from 1 to 1½ quarts.

The portion of the stomach lying above an imaginary horizontal plane passing through the cardiac orifice is called the *fundus* (fig. 202). It is filled with entrapped gas. The more or less vertical portion of the organ below the fundus is called the *body*. The succeeding portion, represented by the hook of the J in the case of the J-shaped stomach, is known as the *pyloric part* (pars pylorica) and consists of a proximal chamber the *antrum* or *pyloric vestibule* and the *pyloric canal* through which the stomach communicates with the duodenum. The notch at the lower end of the lesser curvature formed by

the bending of the pyloric part upon the body, is known as the *incisura angularis*. The pyloric canal is a narrow passage about 3 cm. long around which the circular coat of the stomach is thickened to form the *pyloric sphincter*. The thickening of the muscle causes a projection of the mucosa which is responsible for the narrowing of the digestive tube at this point and for the slight circular depression on its outer surface. The musculature of the stomach is almost completely separated from that of the duodenum by a ring of connective tissue.

THE MOTOR ACTIVITIES OF THE STOMACH

When the stomach is empty its cavity below the upper part of the fundus, which as mentioned above is inflated with gas, is completely obliterated by the apposition of the gastric walls. Food, after passing through the cardia, collects just above the obliterated portion; apparently simply of its own weight it gradually separates the gastric walls, and passes downwards along the lesser curvature into the body and pyloric part of the organ (fig. 203). This passage-way is sometimes referred to as the *magenstrasse*. The fundus and usually the remainder of the stomach above about the middle of the body shows no peristaltic activity. The muscle of this part of the organ is the seat of a weak tonic contraction which is immediately inhibited by the entrance of food into the stomach—*receptive relaxation*, or even by the presence of food in the esophagus (see also p. 488). The pyloric part, on the other hand, constitutes a chamber wherein the food is macerated, fragmented, and thoroughly mixed. Peristaltic waves commencing near the middle of the body of the stomach sweep downwards through the pyloric vestibule. They are shallow and ill-defined at their commencement but become stronger as they descend. They also increase in strength as digestion proceeds and, when this is at its height, bite deeply into the gastric walls. Cole has studied the waves in the human stomach by means of serial roentgenography and cinematographic projection. He describes the peristaltic movement as a band of constriction which becomes well marked in the region of the *incisura angularis* and ends a centimeter or two above the commencement of the pyloric canal. The gastric wave travels more rapidly over the greater curvature than over the shorter distance of the lesser curvature, and according to Cole the constriction on the lesser curvature upon reaching the *incisura angularis* "marks time," while that on the greater curvature

continues on through the antrum. The wave thus executes a sort of wheeling movement.²

Two or more peristaltic waves may be seen at a moment travelling through the lower part of the body and pyloric region; for this reason the X-ray appearance of the actively motile stomach is irregularly convoluted. The waves in their downward journey show rhythmic variations in depth. They might be described as waxing and waning. At one instant they deeply indent the gastric wall and the segments between the annular constrictions are also reduced in diameter. There appears to be a general increase in tone of the gastric wall, the capacity of the entire pyloric region being reduced. At the next instant there is a general reduction in tone, the waves are less intense, the convolutions of the stomach outline less pronounced, and the capacity of the pyloric region increased.

Cole compares these rhythmical alterations in the organ's shape to the cardiac cycle, and speaks of a *gastric cycle*. From the moment that a particular stomach shape appears to the instant when that form again comes into view constitutes a complete cycle of gastric movements. *Gastric systole* is that phase marked by deep indentations made by the constricting rings, and reduction in gastric capacity. *Gastric diastole* is the period during which the contractions having become momentarily weakened show less tendency to deform the gastric outline. (Figure 204 shows a series of roentgenograms representing a gastric cycle. Systole, I to IV inclusive, and diastole, VIII to X, may be readily distinguished). A complete cycle occupies about 15 seconds. Systole occupies $\frac{7}{10}$ of the cycle; diastole

Gastric motility shows great individual variation; in some types of stomach the wave travels very rapidly, completing its journey in from 5 to 15 seconds. In others the wave takes 30 seconds or so to pass from its origin to the pylorus. The slow waves are the more common.

Apart from these individual differences, the motor activity of the stomach is influenced by the chemical characters and bulk of the meal. Fat and its derivatives, fatty acids and soaps, for example, inhibit the movements, reduce the depth of the peristaltic waves, and lower gastric tone. Fat exerts this effect while in the

² Cole maintains that the peristaltic movement is a function of the muscularis mucosa and not of the regular muscular coats. Some support for this view has been furnished by Gordon and Singleton who fastened steel beads to the outer surfaces of the curvatures of the stomach and studied the gastric movements by roentgenography, a barium meal having first been given. Waves were observed at times which did not disturb the alignment of the beads. They conclude that the stomach wall exhibits two types of peristaltic movement, one a vigorous peristalsis, which involves all coats of the stomach and another, a weaker movement, involving the mucosa and muscularis mucosa only.

stomach and also after reaching the duodenum. Ivy and his associates have obtained evidence that the inhibitory effect of fat is mediated through a chalone (see enterogastrone, p. 436). Fat introduced into the stomach by a stomach tube inhibited the movements of a transplanted gastric pouch after a latent period of 5 minutes.

Some of the products of protein digestion in the intestine (e.g., the monoamino-monocarboxylic acids) and hydrochloric acid inhibit gastric tone and peristalsis. This action which is referred to as the *enterogastric reflex* is brought about through the vagus. Sugars in high concentration

a meal has its origin in one or other of such nervous factors as those just mentioned. When food is taken while one is fatigued, anxious, agitated or hurried, disturbances of the normal motor mechanisms of the stomach give rise to unpleasant gastric sensations. The precise manner in which these are set up is not clear, but it is not unlikely that, in some instances at least, with the inhibition of the normal descending waves of peristalsis, reverse waves arise which lead to heartburn, belching and a feeling of discomfort (p. 481). But whatever the mechanism, the relation of psychic factors to gastric symptoms is clearly

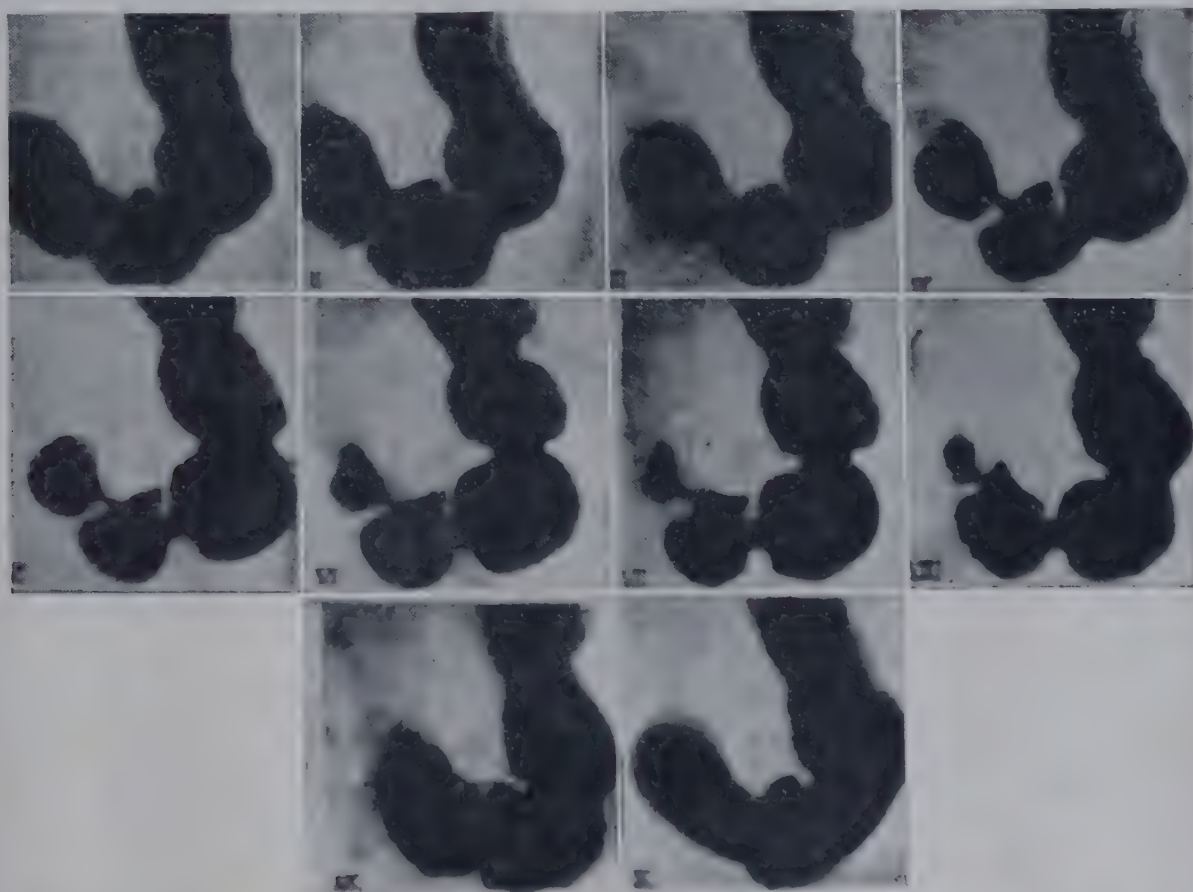


FIG. 204. Serial X-ray photographs of human stomach taken at 2 second intervals during digestion to illustrate a gastric cycle. (From Cole.)

also inhibit gastric movements; this effect is probably induced through the medium of enterogastrone rather than by a reflex mechanism.

In the intact normal stomach distension of the gastric walls acts as a stimulus though extreme distension is inhibitory. Nervousness and anxiety tend to increase peristalsis while certain other emotional states—apprehension, fear, mental strain, shock or depression—tend, as a rule, to inhibit the movements and to reduce gastric tone. Pain and physical fatigue act similarly. Exercise unless very moderate tends to inhibit gastric motility.

It is believed that in many instances the discomfort or distress which follows shortly after

evident. This so-called nervous dyspepsia is, to quote Alvarez, "the disease of the mother who prepares the meal and then wrangles with children or husband at the table; it is the disease of business men and women who gulp down some food at a counter and rush back to work; and it is the disease of the president of a luncheon club, or of the traveling salesman who gives 'pep talks' at luncheons and dinners."

Among chemicals which influence gastric motility the following may be mentioned. Alcohol, lactic acid, coffee, sodium bicarbonate in therapeutic doses, histamine, insulin and choline increase peristalsis; smoking, atropine, vitamin B₁ deficiency (p. 642) infectious fevers

and anoxia depress it. Morphine increases the tone and amplitude of the contractions of the pyloric sphincter; its effect upon the antrum is variable.

THE EMPTYING OF THE STOMACH

After an ordinary mixed meal the normal human stomach empties in from 3 to 4½ hours. A meal consisting mainly of carbohydrate leaves more rapidly than one containing much meat, and this more rapidly than one containing fat. A test meal is evacuated in 2 hours on the average. Fluids and semi-fluids commence to leave the stomach almost immediately after being swallowed (see table 35).

by chloroform and ether and the least by nitrous oxide and cyclopropane.

The rapidity with which raw egg white or whey leaves the stomach, as well as the normal sometimes shortened emptying time in gastric anacidity (p. 740) had always offered obstacles which the acid theory of pyloric control found difficult to surmount. McClure, Reynolds and Schwartz have shown clearly that no important relationship exists between the emptying time and gastric or duodenal acidity. The maintenance of a constant acidity in the duodenum did not prevent pyloric opening. On the other hand, when the duodenum was kept neutral or alkaline by means of fluid introduced through a duodenal

TABLE 35
Gastric evacuation—various foods
(After Wilson)

	MINUTES TO SWALLOW	FIRST LEAVING OF STOMACH <i>minutes</i>	PERCENTAGE OUT OF STOMACH		
			1½ hours	3 hours	4 hours
Carbohydrates:					
Thick porridge.....	2	4	75	95	
Bread 40 grams; dates 100 grams.....	3	3	60	95	
Proteins:					
Egg white, raw.....	1	3	75	85	95
Codfish, boiled.....	5	20	30	85	95
Lean meat, baked.....	5	7	40	80	95
Fats:					
Cream 32 per cent.....	1	1	25	40	75
Bacon and egg yolk.....	5	12	10	30	95
Olive oil.....	1	1	25	50	60

The theory propounded by Cannon, that the pylorus is controlled by the acidities of the gastric and duodenal contents—high gastric acidity causing opening and high duodenal acidity closure—is held no longer. A stimulus of practically any sort arising in the duodenum can reflexly increase the tone of the pyloric sphincter and effect its closure, a high acidity can serve as such a stimulus, but it has no specific effect in this regard. A high degree of alkalinity in the duodenum also inhibits gastric motility and delays evacuation. The emptying time of the stomach is actually shortened by reducing the gastric acidity, as by the ingestion of sodium bicarbonate or of disodium phosphate (Van Liere and Sleeth). Bile salts reduce the emptying time of the human stomach. The emptying time is prolonged by general anesthetics, the greatest increase being caused

by tube, rhythmical opening and closure of sphincter occurred in the usual way. Nor was Baird, Campbell and Hern able to obtain evidence for the acid theory of pyloric control from experiments on human subject. The emptying time of the stomach showed no dependence upon reaction of the gastric or duodenal contents. Essentially similar results have been obtained by McCann and several other investigators.

The opinion is now widely held that the pylorus is patent for the greater part of the time and that the evacuation of the stomach is definitely related to the peristaltic activity of the antrum. Wheelon and Thomas obtained simultaneous records in animals by means of balloons placed respectively, in the pyloric antrum and the pyloric canal, which showed that as the constricting wave traverses the antrum the sphincter becomes

relaxed and the chyme is swept before the wave into the duodenum. The pylorus then closes for a moment, relaxing again and remaining open until the next wave of constriction arrives from the antrum. Graphic records obtained by means of balloons placed in the antrum combined with X-ray examination also show that the emissions of chyme through the sphincter are coincident with the passage of waves over the former region (Carlson and associates), and Baird, Campbell and Hern found that in the human subject fluids shortly after being drunk issued from a tube placed in the duodenum just beyond the pylorus not continuously, but in jets. According to Cole's description, the pylorus closes at the end of gastric systole (p. 484), remains closed during the commencement of diastole, but then relaxes and remains relaxed during the greater part (nine-tenths) of the gastric cycle. The importance of the pylorus (the keeper of the gate) in controlling gastric evacuation has, therefore, been greatly exaggerated. X-ray examinations of the stomachs of patients in whom the pylorus has been excised, show emptying times which do not differ significantly from the normal (Singleton).

It is apparent from the foregoing discussion that factors which increase or diminish *gastric tone* and the *force of the antral contractions*, will shorten or lengthen, respectively, the evacuation time. The immediate factor which determines the rate of gastric evacuation appears to be the pressure gradient between the antrum and the duodenal bulb. Fat, for example, inhibits gastric motility and so delays the emptying time.

The degree to which the gastric contents have been reduced to *fluid or semi-fluid consistency* appears also to be an important factor determining the rate of emptying of the stomach. As already mentioned, water drunk by the human subject passes through the pylorus in squirts almost immediately after having been drunk. In the early stages of digestion, when the food contains pieces of solid material, the tone of the pylorus is higher than in the later stages, when the gastric contents are in a semi-fluid state. Raw egg white and fluid milk also leave more rapidly than coagulated egg-albumin or clotted milk. The shorter emptying time of carbohydrate food as compared with protein is due probably to the greater readiness with which the former is reduced to a semi-fluid state. The details of the mechanism whereby the consistency of the food and the emptying rate are correlated are not clear, unless, as has been suggested, solid particles act as mechanical

stimuli which cause pyloric closure and possibly set up retrograde waves in the vestibule. Cannon fed pellets of a bismuth salt to an animal and, observing the gastric movements by means of the X-ray, saw the opaque particles carried up to the pylorus by peristaltic waves. They were not, however, allowed to pass into the duodenum but were returned to the vestibule. They were retained in the stomach after the rest of the gastric contents had been discharged. Retrograde waves in the vestibule have also been observed by Kleine and others when solid materials such as undigested meat came into contact with the mucosa in the region of the pylorus.

The observations of Apperly and several other investigators indicate that the *osmotic pressure* of the gastric contents is another factor influencing the emptying time of the stomach. Macleod and associates found that hypertonic glucose solutions when fed to rats were reduced to isotonicity before evacuation occurred, and McSwiney and Spurrell observed that hypertonic meals delayed gastric evacuation, proportionately to their hypertonicity.

Finally, *the state of the upper part of the duodenum* (p. 490)—its fullness or emptiness, which thus alters the pressure gradient between the antrum and the duodenal bulb—has also a pronounced effect upon the state of the pyloric sphincter and the emptying time of the stomach. It has been mentioned on page 485 that certain digestive products in the duodenum cause gastric inhibition through the enterogastric reflex or through the liberation of enterogastrone.

The main factors, therefore, which influence the emptying time of the stomach are: (a) the motility of the stomach itself, (b) the consistency of the gastric contents, (c) the osmotic pressure of the gastric contents, and (d) the quantity of material in the duodenum. It should be remembered that the pressure in the antrum must exceed that in the duodenum in order for the stomach to empty. Gastric evacuation is also influenced to some extent by the position of the body, emptying being more rapid when the subject is lying upon his right side than when standing or recumbent upon his left side.

INTRAGASTRIC PRESSURES

The pressure within the human stomach varies in the standing or sitting position from 6 to 10 cm. H₂O. In certain other positions, as shown by Wilson and Irving, e.g., stooping or lying on the right side, the pressure is frequently subatmospheric (−1 to −5 cm. H₂O). The

pressure in the fundus is considerably lower than that in the pyloric part. This indicates that the tonic contraction of the fundic walls does not serve to press the food towards the pylorus, as has sometimes been supposed. In the dog, intragastric pressures up to 90 cm. of water have been observed. The pressure is usually higher in the antrum than in the duodenal bulb. The intragastric pressure varies with the intra-abdominal pressure and with the respiratory movements.

As already mentioned, the entrance of material into the stomach causes a reduction in the tone of the gastric musculature, and an increase in the capacity of the stomach for the accommodation of the ingested food or drink (see postural tone, p. 477). If, for example, a large quantity of water be drunk the upper surface of the fluid in the stomach as shown by X-ray rises very slowly and, after reaching a point about the middle of the body, remains practically stationary at this level; though an additional quantity of fluid be drunk, little change in the level of the fluid occurs. Ordinarily, the intragastric pressure shows no increase after the ingestion of a meal; and even after a liter or so of water has been swallowed no rise in pressure, or only a very transitory one, can be detected. Conversely when fluid is withdrawn from the stomach the gastric capacity becomes automatically reduced and the intragastric pressure remains practically unaltered. The adjustment of the gastric capacity to the volume of the food appears to be dependent in part at any rate upon a central reflex. According to Kelling it is abolished by deep anesthesia. Adaptation is shown, however, to some extent even by the excised stomach. The increase in gastric capacity is accompanied by reflex relaxation of the abdominal muscles. If, on the other hand, an amount of fluid which when taken into the dog's stomach causes no change in intragastric pressure is injected into the peritoneal cavity, relaxation of the abdominal muscles does not occur and the intra-abdominal pressure rises in proportion to the volume of the fluid which has been introduced. The intragastric pressure rises, of course, to a corresponding degree. The discomfort and sensation of fullness after a meal eaten hastily or under conditions of nervous strain are attributable in many instances to the inability of the gastric wall and abdominal muscle to become accommodated rapidly enough to the increased volume of the stomach contents.

THE INNERVATION OF THE GASTRIC MOVEMENTS

The stomach contains intrinsic plexuses (of Auerbach and Meissner) similar to those in the intestine (p. 501). Its extrinsic innervation is through both the right and left vagus nerves and the sympathetic (fig. 205). The fibers of the vagus end around cells in Auerbach's plexus.¹

¹ Both vagus nerves enter into the formation of the esophageal plexus. From the latter, two trunks, each of which contains fibers from the right and the left vagus, emerge. The anterior vagal trunk supplies the anterior surface of the stomach and the posterior trunk

The postganglionic fibers of the sympathetic (cell stations in celiac ganglion) end by arborizations around the muscle cells. The effects of the experimental stimulation of either of these nerves cannot always be predicted. Vagal stimulation may cause either augmentation or inhibition of gastric motility. Inconstant effects are also caused by sympathetic stimulation. The result obtained depends upon several conditions, e.g., the frequency and strength of stimulus, the level of the tone of the muscle at the time and the activity of the peristaltic movements. Generally speaking, when the tone of the gastric muscle is high, inhibitory effects are produced by vagal stimulation, whereas in states of low tonus a motor effect is obtained. McCrae and McSwiney and Stopford found that when the *rhythmical movements* were present in the antrum, vagal stimulation caused inhibition but, if the movements were absent, vagal stimulation initiated them. Similarly in the case of the sympathetic, when hypotonus or hypertonus pre-exists, stimulation causes augmentation or inhibition, respectively, of gastric motility. Inhibition of the rhythmical movements of the antrum most frequently follows sympathetic stimulation but again the result is not predictable; increased activity may result. The sympathetic is generally considered to be inhibitory to the pyloric sphincter and the vagus excitatory, but an opposite effect may be obtained from either nerve, the tonus level at the time appearing to be a determining factor. Though variability of response is quite evidently a characteristic of the gastric nerves, their functions can be summarized in the statement that *the vagus is predominantly motor, the sympathetic predominantly inhibitory*. Thomas and Crider observed that, in dogs, vigorous gastric peristalsis ceased immediately upon sectioning the vagus nerves; the stomach remained quiescent for hours. But when the sympathetic nerves are sectioned, as well, although there is inhibition of peristalsis for a time, motility soon returns. This suggests that a tonic inhibitory influence, exerted by the sympathetic innervation is responsible for the abolition of gastric motility when the vagi alone are sectioned. In man, decrease in tone and in the motility of the stomach and reduction in the tone of the pyloric sphincter

the posterior surface. Each aspect of the stomach thus receives fibers from both vagus nerves. The pylorus and first part of the duodenum receive a special branch which arises from the anterior trunk. This branch also sends twigs to the liver. The posterior trunk supplies a large branch to the celiac plexus. (See McCrae)

have been reported to result from section of the gastric vagi. On the other hand, section of the

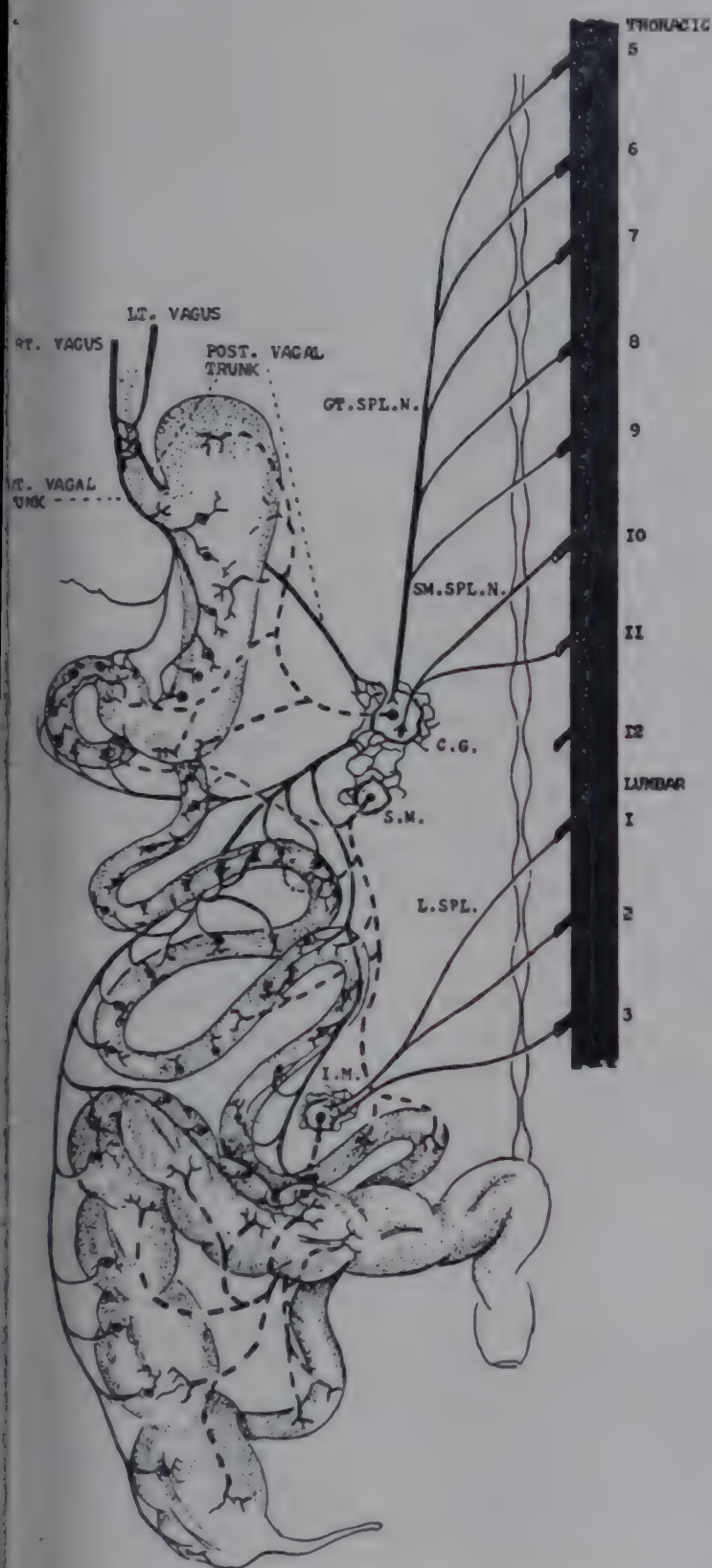


FIG. 205. Diagram of the innervation of the stomach, small intestine and proximal part of the colon. GT. SPL.N., great splanchnic nerve; SM. SPL.N., small splanchnic nerve; L. SPL., least splanchnic nerve; C.G., celiac ganglion; S.M., superior mesenteric ganglion; I.M., inferior mesenteric ganglion. Continuous lines, vagal and sympathetic preganglionic fibers; broken lines, sympathetic postganglionic fibers; ganglion cells and postganglionic fibers of vagus in gastro-intestinal wall.

sympathetic innervation has been found to increase the motility of the human stomach. The innervation of the cardia is discussed on page 481.

After section of both sets of extrinsic nerves to the stomach, motility is abolished but returns after a time, the movements then being governed by the intrinsic nervous mechanisms. The evidence for the liberation of acetylcholine by vagal stimulation is given on page 948. The gastric vagi also contain afferent fibers. Section of one vagus and stimulation of its central end is followed by movements of the stomach.

Evidence for a diencephalic center for gastric movements has been obtained by Beattie and Sheehan. Stimulation of the hypothalamus in the region of the tuber cinereum resulted in contractions of the stomach; the effect was abolished by section of the vagi. Stimulation of the posterior hypothalamic region, on the other hand, inhibited all gastric movements. Sheehan in a later communication reports that cooling or faradic stimulation of the frontal or premotor area of the cortex in the monkey inhibited the movements of the stomach which had been contracting actively. Contractions could not be initiated in a resting stomach by stimulation of the cortex.

ACUTE DILATATION OF THE STOMACH

In this grave though comparatively rare condition the stomach becomes greatly, sometimes enormously, distended; its cavity contains large quantities of fluid and gas which may stretch its walls to paper thinness. The accumulated fluid of course represents a corresponding loss of water and chloride from the body's stores. Reduction in blood chloride, alkalosis and dehydration result (p. 511); tetany may occur (p. 701). There is profound prostration; collapse ending in death is not uncommon. The condition, in the majority of instances, occurs as a sequence of an abdominal or pelvic operation but it occasionally follows a blow upon the abdomen, some severe injury, childbirth, a drinking bout or overeating.

The condition is apparently of reflex origin, the initial and essential factor being the loss of gastric tone. The stomach then becomes distended by the accumulation of its own secretions which it is unable to expel, as well as by the regurgitation of fluids from the duodenum. Even the normal stomach and also probably the upper part of the duodenum cannot absorb the fluids which they secrete, so if the gastric secretions do not leave the stomach they simply collect and gradually increase in volume. Hypersecretion, apparently, is not a factor in the early stages at any rate. Later, however, the distension of the gastric walls probably acts as a stimulus to secretion (p. 433). In some instances, swallowed air and intestinal gases play a part in ballooning the relaxed organ. According to Dragstedt when the dilatation reaches a certain degree an added factor comes into

play; the enlarged stomach by its pressure obstructs the third part of the duodenum.

THE DUODENAL BULB OR CAP

The first two inches of the duodenum are referred to as the duodenal bulb or cap; this region is of special interest since it is the site of duodenal ulcer (p. 444). Functionally, the duodenal bulb is considered by most observers as part of the stomach. It is somewhat triangular in outline with its base surmounting the pylorus and is directed backwards, upwards and to the right (fig. 202). Its glands (Brunner's) secrete an alkaline fluid. Its junction with the duodenum proper is marked by a slight thickening of the circular muscle fibers which are believed by some to exert a sphincter-like action. During the period of gastric evacuation the bulb becomes filled with chyme. From time to time a peristaltic wave sweeps over it from base to apex, carrying its contents into the next section of the duodenum. The chyme is also conveyed into the duodenum proper in a passive manner, that is, by the simple overflowing of the bulb. Occasionally an antiperistaltic wave arises in the duodenum below the cap, continues upwards to the pylorus and appears in the pyloric vestibule.

Related movements of the pyloric vestibule, pyloric sphincter and the duodenum below the bulb

Wheelon and Thomas placed recording instruments in the pyloric antrum, pyloric canal, and duodenum distal to the cap, and obtained simultaneous tracings of the contractions in these three situations. The movements of the antrum and sphincter were found to be related with those of the duodenum. During the contraction of the antrum the duodenum is relaxed, but about one minute after the commencement of the relaxation of the vestibule the duodenum commences to contract. That is, relaxations of the vestibule roughly coincide with contractions of the duodenum and contractions of the antrum with relaxations of the duodenum (receptive relaxation of the duodenum). Contractions of the sphincter were found to occur rhythmically from 3 to 5 times per minute, each contraction commencing while the duodenum was relaxed. The contraction of the duodenum commenced $2\frac{1}{2}$ seconds later but the contractions in the two situations reached their maximal heights at about the same time. These movements of stomach and duodenum are correlated apparently through the intrinsic plexuses in the gastrointestinal wall. A connective tissue barrier exists between the muscle of the stomach and duodenum which must prevent the continuous spread of the wave independently of a nervous mechanism of some sort.

Movements initiated in the duodenum have been

shown, on the other hand, to influence the activities of the sphincter. When the duodenal mucosa was stimulated an ordinary peristaltic wave appeared which travelled down the bowel in the usual way (p. 496), but a firm contraction of the sphincter also occurred, followed by a prolonged period of relaxation. A series of such stimuli produced a continuous contraction of the pyloric sphincter. Activity of the duodenum has been shown by several observers to have the effect of increasing the tone of the sphincter. The state of the duodenum in this way affects indirectly the emptying of the stomach, and the filling and emptying of the cap. When the duodenum is filled with chyme active movements are set up in its wall which have the two-fold effect of withdrawing material from the cap and causing reflex closure of the sphincter. When the duodenum becomes empty its activity subsides, the pylorus relaxes more fully and the emptying of the stomach is hastened. This effect of a full duodenum upon the emptying time of the stomach is shown by the fact that a meal taken after a period of fasting is discharged much more rapidly than if the duodenum is already replete with chyme; gastric evacuation is then delayed. Distension of the bowel by a balloon or its irritation by chemical or mechanical means increases pyloric tone. It has been shown repeatedly on the other hand that if the chyme as it issues from the pylorus be allowed to escape through a fistulous opening instead of being permitted to fill the duodenum, the stomach empties with greater speed. It has been found by Thomas, Crider and Mogan that a reflex effect of even greater importance than that upon the sphincter is exerted from the duodenum upon gastric peristalsis. Substances introduced into the duodenum markedly reduced the force of the peristaltic waves in the antrum, whereas draining the duodenum increased gastric motility and hastened gastric evacuation.

Antiperistalsis in the second and third parts of the duodenum

Antiperistalsis is a normal occurrence in the duodenum below the cap, the reverse waves can be seen during X-ray examination of the human subject passing orally and conveying material to a higher level of the duodenum, into the cap or through the pylorus into the stomach.

VOMITING OR EMESIS

The mechanism of vomiting involves the co-ordinated actions of the muscles of the stomach, esophagus, and abdominal wall. The act may also be associated with antiperistaltic movements in the intestine. The muscular mechanisms are governed by a center in the medulla, which discharges impulses along numerous efferent nerves, and may be influenced by afferent impulses arising in the stomach, in other viscera or in practically any region of the body. Or, the center

may be excited by substances conveyed in the blood stream (p. 493).

THE VOMITING MOVEMENTS

Cannon has given a graphic account of the act of vomiting in the cat. The movements were observed by means of radiography after a bismuth meal and the administration of apomorphine, which excites the vomiting center. The upper part of the stomach showed complete inhibition of its tone and appeared as a perfectly flaccid bag; the cardia relaxed. There then followed several deep peristaltic contractions which, commencing about the middle of the body of the organ, swept downwards toward the incisura angularis where they came to a standstill forming a sharp ring of constriction. From this point a weaker wave continued to the pylorus. Finally, a very deep, strong contraction at the incisura appeared to almost divide the stomach in two, the cardiac pouch and the cardia meanwhile remaining quite relaxed. A sharp contraction of the diaphragm and abdominal muscles then followed and ejected the gastric contents through the open cardia into the esophagus. The stomach played a more or less passive part in the process,⁴ its evacuation being effected by the strong compression to which it was subjected by the sharp descent of the diaphragm and the contraction of the abdominal muscles. Antiperistalsis was observed only once and then the wave did not proceed beyond the antrum. The deep contraction at the incisura offered an effectual barrier to the passage of stomach contents in a downward direction.

During the ejection of the vomitus the esophagus is relaxed throughout; the glottis is closed and the respirations are inhibited, the larynx and hyoid bone are drawn forward and are held rigidly in this position. The throat is thus enlarged to allow free exit for the stomach contents which are prevented from entering the naso-pharynx by the elevation of the soft palate.

Similar movements have been described in man. Definite antiperistaltic waves in the stomach are rarely seen, though violent churning movements may occur.⁵ According to Barclay, just

⁴ Magendie showed long ago that an active gastric element was not necessary for the vomiting act, since its essential features could be induced in animals after the stomach had been replaced by a pig's bladder.

⁵ In certain lower forms, however, e.g., the fish and the frog, which of course have no diaphragm, vomiting is carried out by the activity of the stomach alone, antiperistaltic waves carrying the food through the cardia. This more primitive type of vomiting, i.e.,

prior to the commencement of the vomiting movements, a sudden reduction of gastric tone occurs, the lower limit of the stomach dropping a couple of inches. This coincides with the sensation of nausea (p. 519) which ordinarily precedes vomiting. In certain types of vomiting, e.g., intestinal obstruction, or in persistent vomiting from other causes, antiperistalsis arises in the small intestine and sweeps material into the stomach or there may be a strong contraction of the duodenum which reverses the pressure gradient between the antrum and the duodenal bulb. Such movements of the duodenum occur some time prior to the actual vomiting or at the same time; it accounts for the fact that a short time after the stomach has been thoroughly washed out, bile-stained fluid or fecal material may be vomited. According to Alvarez, reverse peristalsis starting in the upper bowel is itself a potent cause of nausea and vomiting.

Relaxation of the cardia is an essential part of the vomiting act, for the stomach is subject to strong compression during coughing, defecation, etc., yet the gastric contents are not as a rule forced into the esophagus. The tone of the cardia is probably actually increased at these times. It has been mentioned that division of the vagi in animals causes the cardia to enter into a spastic state. Hatcher and Weiss found that if after such a procedure a vomiting reflex was initiated, mucus was expelled from the esophagus and the usual muscular movements were called into play, with the exception of relaxation of the cardia. That is, the animal retched but material was not expelled from the stomach. It is well known that with some persons vomiting is difficult while in others little distress is experienced. Differences in the degree of tone of the cardia are probably responsible for these individual peculiarities.

THE VOMITING CENTER

The vomiting center lies in the medulla in the neighborhood of the dorsal nucleus of the vagus nerve (p. 861). It is close to but distinct from the respiratory center. Vomiting is impossible after this area has been destroyed. The essential and accessory movements involve so

where reverse peristalsis and relaxation of the cardia are the prominent features, occurs normally in infants. The excess fluid of an oversized meal is regurgitated without the assistance, apparently, of the abdominal muscles or diaphragm; position and external pressure upon the abdomen following the meal sometimes, no doubt, also play a part.

many muscles that the center as in the case of the swallowing center probably serves the purpose of a receptive station for afferent impulses and a "control board" for various motor cranial nuclei. The *efferent* fibers are contained chiefly in the phrenics, the vagi and the sympathetics, but fibers are also conveyed by spinal nerves to the abdominal muscles and by cranial nerves to the muscles of the pharynx, palate, etc. The *afferent* impulses reach the center along a multitude of routes, the chief being the vagal and sympathetic fibers of the stomach and abdominal viscera.

THE INDUCTION OF VOMITING

The vomiting center may be excited (a) reflexly by impulses arising in the stomach, or some other part of the body, (b) by impulses received from cerebral centers, or (c) by chemical materials carried to it in the blood stream.

Vomiting of reflex and psychic origins

Mechanical and chemical irritants of various kinds act upon vagal or sympathetic afferent terminals in the gastric mucosa and initiate the vomiting reflex. Toxic materials taken in the food or formed during digestion may act in this way. Among the specific excitants of the vomiting act—*emetics*—are tartarate of antimony (tartar emetic), mustard, ipecac, mercuric chloride, copper and zinc sulphates, etc. Some of these have a selective action upon the terminations of one or other of the two groups of afferent autonomic fibers. For instance, tartar emetic, in the stomach, acts through the vagus but not through the sympathetic, since it fails to act after vagotomy, or after the vagal effect has been annulled by atropine. Mercuric chloride, on the other hand, acts more especially on the sympathetic mechanism since atropine does not prevent its emetic action, but ergotoxine which acts specifically by paralyzing sympathetic fibers, does. Mustard, salt and water, copper sulphate and zinc sulphate act upon both types of nerve.

Impulses arising from structures other than the stomach, particularly from other parts of the alimentary canal, are also powerful excitants of the vomiting center. It is well known that even mild mechanical stimulation of the pharynx or fauces is effective. Inflammation or mechanical disturbances in the intestine, e.g., appendicitis, obstruction, strangulation, etc., may induce violent emesis. Distension of the duodenum in a conscious animal induces vomiting movements.

Impulses arising in the kidney, bladder, uterus, gall-bladder, heart or any other viscus may induce vomiting quite independently of any condition within the stomach itself. Hatcher and Weiss have shown that several substances cause emesis through their action upon the heart, e.g., digitalis in large doses and pilocarpine. These drugs act apparently upon both vagal and sympathetic mechanisms. Tartar emetic also acts through the cardiac vagus as well as through the gastric nerves. These facts afford an explanation of the nausea and vomiting that occur in heart failure and in disease of the coronary vessels. Table 36 gives a summary of the afferent fibers involved in the vomiting reflex and the susceptibility of the two sets of fibers to the action of several drugs.

Severe pain, wherever located, strong emotion or impulses arising in the organs of special sense,

TABLE 36

DRUGS	AFFERENT AUTONOMIC FIBERS ACTED UPON	ORGANS CONTAINING SUSCEPTIBLE FIBERS
Mercuric chloride	Sympathetic and vagus	Stomach
Tartar emetic	Vagus	Stomach, duodenum and heart
Digitalis	Sympathetic and vagus	Heart
Pilocarpine	Sympathetic and vagus	Heart

e.g., those of smell, taste or sight, may cause vomiting. In the dog a *conditioned vomiting reflex* may be readily established by morphine injections (p. 908). Stimulation of the nerve terminals in the vertical semicircular canals (vestibular nerve) is considered the most potent factor in the causation of sea sickness, though impulses arising in the stomach itself or the retinae are contributory. In animals, the vomiting reflex is inhibited by certain other reflexes, e.g., the scratch and defecation reflexes. In man, the activity of the cerebral centers, e.g., sensations of disgust, anxiety, apprehension, worry, etc., enhance the tendency to sea-sickness, whereas interest or attention tend to prevent it. Benzadrine is among the best drugs in use for its prevention (see Albrecht).

"CENTRAL" VOMITING

Certain substances such as *apomorphine*, *emeline*, *picroltoxine*, when administered intravenously cause

vomiting through a specific action upon the center. These substances induce vomiting in animals when applied directly to the center. Typical vomiting efforts (retching) follow the injection of apomorphine after removal of the stomach and intestines. Emetics of this type are believed, however, to exert their effect by raising the excitability of the center rather than by direct stimulation of the nervous tissue. This is not merely an academic distinction but is of considerable interest from a practical point of view. Such an action is comparable to that in which strychnine acts upon the spinal centers. It implies that substances formed in the body in disease may raise the excitability of the vomiting center to a level where afferent impulses, ordinarily of sub-threshold value, may become effective for the initiation of the reflex.⁶ In other words, the so-called central type of vomiting is also essentially of reflex origin. General bodily conditions, e.g., mental stress, hysterical states or fatigue, may act similarly upon the excitability of the center. It is evident then that vomiting does not necessarily imply a primary disturbance of the gastrointestinal tract.

The persistent of pernicious *vomiting of pregnancy* is probably due to increased excitability of the center resulting from some metabolic disturbance. According to Harding the important factors in its production are carbohydrate starvation and dehydration with ketosis. Ordinary morning sickness is looked upon as a minor form of this condition, and differing from pernicious vomiting only in degree. As a result of the demands of the fetus, liver glycogen is low during pregnancy. After the fast of the night the reserves of carbohydrate are further reduced; a mild ketosis results which leads to nausea and vomiting. The distaste for food by hindering the replenishment of the carbohydrate stores aggravates the ketosis. Thus morning sickness merges insensibly into the pernicious type of vomiting. A neurotic element is also frequently a potent influence in the development and persistence of the condition. The obvious corrective measures are, high carbohydrate feeding, the free administration of fluids, injections of glucose if necessary, mild sedatives, rest and quiet.

Interference with the blood supply to the center, as by elevation of the intracranial pressure through tumor, etc., or by anemia or hemorrhage, may

⁶ It is of interest in this regard that substances formed in the body, e.g. adrenaline, choline, and histamine induce vomiting when applied directly to the center.

raise its excitability to the point where vomiting ensues. Vomiting associated with raised intracranial pressure occurs suddenly, is forceful and not preceded by nausea (projectile vomiting). Vomiting may be induced in animals by tying the carotid and vertebral arteries. The vomiting of mountain sickness is also a phenomenon associated with anoxemia (p. 360).

THE MOVEMENTS OF THE STOMACH IN HUNGER

The movements of the stomach during fasting have been studied by a number of observers, including Cannon and Washburn, and Carlson. The latter observer, in an exhaustive series of experiments has investigated the contractions and tonus changes of the empty stomach in various species of animals and in man. The movements were recorded by means of a thin rubber balloon introduced into the stomach and connected by tubing with a manometer containing water, chloroform or bromoform. A float placed upon the surface of the fluid carried a writing point by means of which the contractions were recorded upon a moving surface (fig. 206).

In man the movements of the empty stomach are of two types: (a) a *tonus rhythm* of the fundus and body and (b) the *hunger contractions* (fig. 207).

The tonus rhythm

The tone of the fundus and body of the stomach increases steadily as digestion progresses. When the stomach has been nearly emptied the tone is near its maximum, and shows rhythmical fluctuations. The tonus changes are never very marked features and require a rather delicate recording instrument to make them evident. They were not recorded in the earlier experiments of Cannon and Washburn. They have been observed directly by Carlson through a gastric fistula in man when the stomach was practically empty of food and contained no balloon or other foreign material. The rate of the tonus waves is slow, but very regular. They have a frequency of about 3 or less per minute.

The hunger contractions

These are powerful peristaltic waves which arise in the cardia and include the entire stomach. They commence about three hours after a meal, i.e., when the stomach is nearly empty, and are superimposed upon the tonus rhythm. The hunger contractions do not occur continuously,

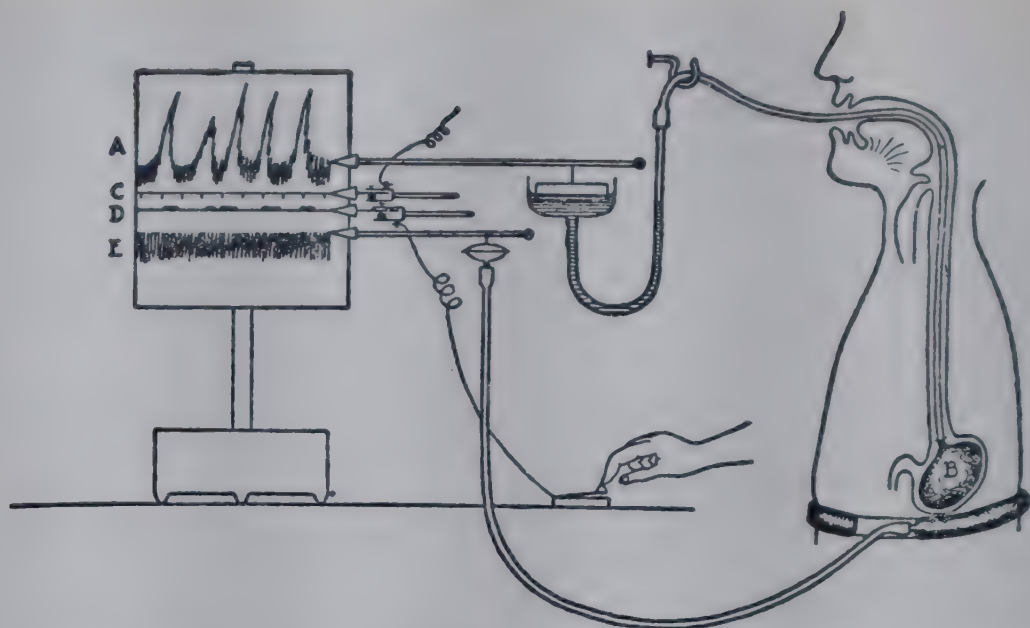


FIG. .206 Diagram showing the method used to record the gastric hunger contractions. A, kymograph record of the increase and decrease of volume of the gastric balloon B; C, time records in minutes; D, record of the subjective experience of hunger pangs; E, record of the pneumograph placed about the waist. (From Cannon.)

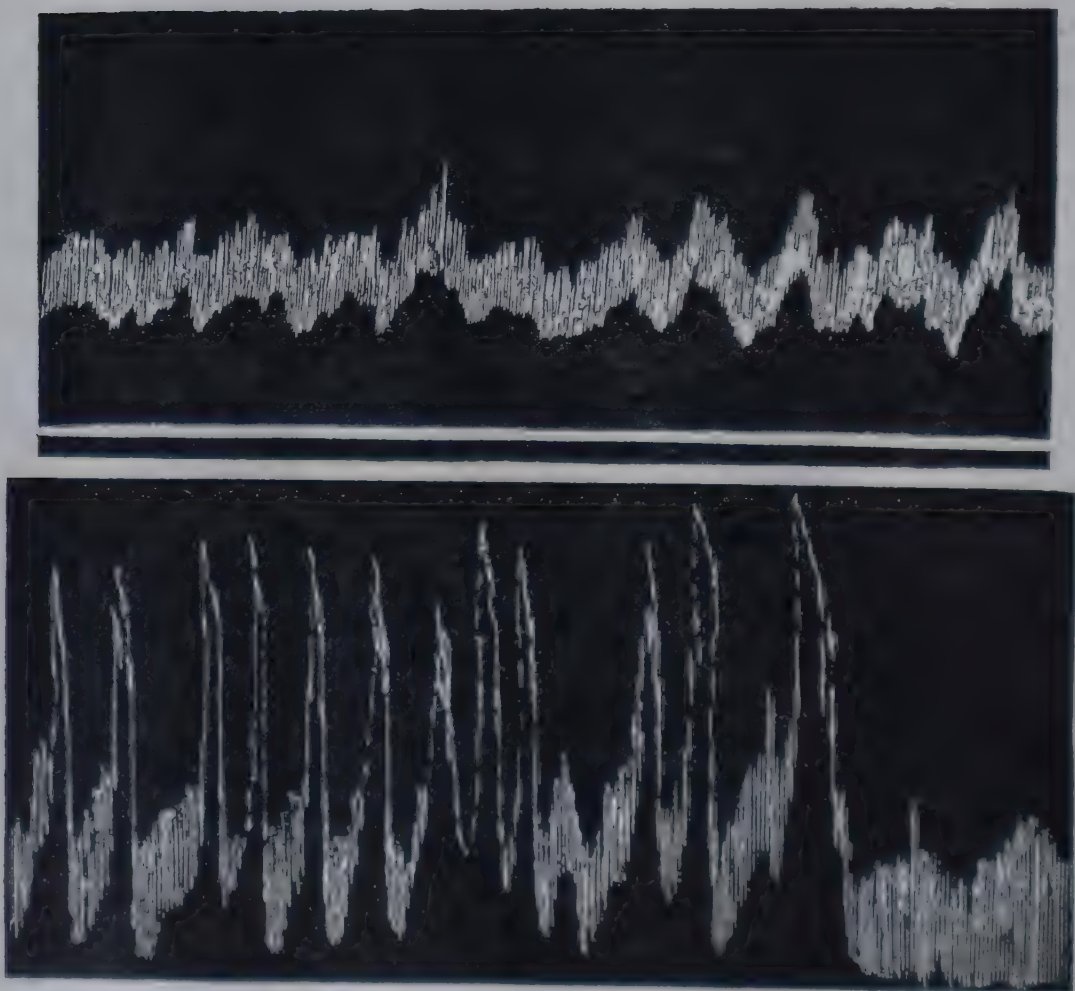


FIG. 207. Upper, tracing of the tonus rhythm of the stomach (man) three hours after a meal. Lower, tracing from the stomach during the culmination of a period of vigorous gastric hunger contractions. (From Carlson)

but in series (hunger periods) separated by intervals in which the stomach, except for the tonus rhythm, is quiescent. The duration of each hunger period is usually from 30 to 45 minutes though it may continue for 1½ hours or be as short as 6 minutes.

The longer periods are found when the tonus of the fundus is high, the shorter ones are associated with a low tonus. The quiescent intervals last from $\frac{1}{2}$ to $2\frac{1}{2}$ hours. The duration of individual contractions is from 20 to 25 seconds, and their amplitude varies throughout the series. They are relatively feeble at the commencement, but become of maximal strength about the middle of the hunger period and die down again toward the end. Their frequency increases progressively throughout. At the beginning of the period they occur several minutes apart, but toward the end they succeed one another rapidly so that the intervening pauses are practically abolished and the muscle may pass into incomplete tetanus which usually lasts for from 2 to 5 minutes, but may be as long as 15 minutes. It occurs especially in young robust individuals, being unusual in older persons. Discomfort or actual pain (hunger pang) is associated with the contractions. In infants the tonus rhythm and the hunger contractions have been demon-

strated shortly after birth and before the stomach has been filled. When the contractions become well marked the infant wakes and cries.

During a fasting period in the human subject investigated by Carlson extending over a five-day period the hunger contractions showed no diminution. They, as well as the tonus rhythm, actually increased in amplitude, yet the hunger pangs and the general sensation of hunger became less after the third day. It is well known that the subjects of prolonged fasts experience little discomfort after the first few days and even the desire for food may pass.

The hunger contractions were found by Carlson to be inhibited by various means, e.g., smoking, compression of the abdomen, as by "tightening the belt," taking a quantity of water into the stomach, strenuous muscular exercise, and the application of cold to the surface of the body.

CHAPTER XLIV

MOVEMENTS OF THE ALIMENTARY CANAL (*Continued*); ABSORPTION FROM THE INTESTINES; THE FORMATION OF FECES; CONSTIPATION; INTESTINAL OBSTRUCTION

MOVEMENTS OF THE SMALL INTESTINE

Three types of muscular movements are usually described as occurring in the small intestine: (a) *peristalsis*, (b) *segmenting contractions*, and (c) *pendular movements*.

PERISTALSIS

This type of movement has already been mentioned as occurring in the esophagus and stomach. From a study of the peristaltic wave in the bowel Bayliss and Starling formulated the "*law of the intestine*," which states that a stimulus applied to a given point in the intestinal wall initiates a band of constriction on the proximal side and relaxation on the distal side of the stimulated point. The two phases, contraction and relaxation—excitation and inhibition—were described as traveling down the bowel at the same rate, constituting a wave which swept the intestinal contents before it. It is questionable, however, whether relaxation of the bowel on the distal side of the stimulated point actually occurs. Henderson was unable to demonstrate it in the intestine of either the guinea-pig or rabbit, a simple constricting ring being the only movement observed. The natural stimulus to peristalsis and other types of intestinal movement is the distension of the intestinal wall caused by the food mass within its lumen. Quigley and associates have shown that a bolus is propelled along the bowel in a spiral fashion. They inserted a bolus of cotton to which two long threads of different colors were attached and found that the rotation occurred in an anti-clockwise direction. The length of bowel traversed in making a full rotation (360°) was from 23 to 35 cm. The bolus was propelled along the intestine (ileum) at an average rate of 9 cm. in 8 or 9 minutes.

It has been mentioned that waves may be seen passing in an oral direction (antiperistalsis) in the duodenum (p. 490). For a variable distance above the ileocolic valve antiperistalsis also occurs, and appears to serve as a check to the too rapid passage of ileal contents into the cecum. With these exceptions, peristalsis normally travels only in an aboral direction. That the small intestine

for the most part is incapable of transmitting peristaltic waves in the opposite direction was demonstrated by Mall. He resected a segment of the small bowel and then restored the continuity of the tube by suturing the resected portion in the reverse position. Peristaltic waves travelled from below upwards in the reversed loop, and obstruction occurred due to the accumulation of food at the upper suture line. Cannon in a similar experiment also observed that the reversed loop offered a barrier to the passage of the food. He saw, in addition, the food carried toward the pylorus in the normal segment of intestine above the loop. This latter observation is in accord with the belief that reversed peristalsis occurs in pathological conditions, e.g., intestinal obstruction, and is responsible for the passage of fecal material into the stomach. It should be mentioned, however, that if the reversed loop be quite short peristaltic waves arising in the normal bowel above may simply push material through it as though it were an inert tube. Also it has been reported that if the animal survives the operation for a sufficient length of time (several weeks), the reversed segment may adapt itself to the altered conditions and move the food downward by true peristalsis (i.e., antiperistalsis in so far as the inherent ability of the bowel is concerned).

In animals examined by means of X-rays, peristalsis is not as a rule of frequent occurrence and when waves do appear they follow, not in a regular series, but at odd intervals. The peristaltic movements are of two types. *First*, a slow, gentle wave which moves sluggishly along the bowel at a rate of from 1 to 2 cm. or less per minute, may be seen from time to time. This transfers food masses, which have already been subjected to the more active segmenting movements, for short stretches along the intestine. *Secondly*, a swiftly moving peristaltic wave appears from time to time and coursing down the bowel for longer or shorter distances, sweeps all before it and then dies out. The food is left for a later wave to carry it further; the food is thus conveyed along the bowel in relays. This type of movement is spoken of as the "*peristaltic rush*." Its speed

may be anywhere from 2 to 25 cm. per second, the farther it goes the greater speed it attains; the average rate is about 10 cm. per second. The length of bowel traversed by any wave varies in accordance with the general state of activity of the bowel at the time and with the strength of the stimulus. After a strong cathartic, or as the result of some intense stimulation of the gastrointestinal tract as by an irritant poison, for example, the wave may sweep with great rapidity from pylorus to anus, completing the entire journey in a minute or less.

Experiments made upon animals show that a rush may be initiated by conditions within the stomach or even by an act of swallowing, and one of the most effective means of producing such a movement in the intestine is to have the animal drink. In some instances the rush is evidently started by the passage of material through the pylorus into the duodenum, but in many others, though a peristaltic wave appears in the stomach this does not reach the pylorus before a rush commences in the duodenum. This fact, and the observation that a swallowing act alone will start a rush indicates that in many instances the mechanism is essentially reflex in nature. A peristaltic rush in the small intestine is frequently followed by a similar though independent movement (mass peristalsis) in the colon (p. 499).

In the human duodenum, following a barium meal, peristalsis is not a prominent feature. Yet the duodenal contents are, nevertheless, being constantly moved onwards. Barclay suggests that this is due to contraction of the muscularis mucosae, the mucous membrane being raised into transverse fold which ripple along the lumen of the bowel.

THE SEGMENTING MOVEMENTS

When the abdomen of an animal is opened and the coils of intestine floated upon a warm saline bath in order to obviate the effects of cooling and drying, rhythmical contractions of the bowel wall may be seen. The movements consist of simple constrictions of the tube, resulting from sharp contractions of the circular coat of the bowel. The annular constrictions do not progress along the bowel, and cause little or no translation of the food.

According to Cannon the segmenting movements in an animal given an opaque meal and examined radioscopically appear in groups of simultaneous constrictions spaced regularly along the bowel.

The groups succeed one another rhythmically at the rate of from 20 to 30 per minute. They divide the intestinal contents into numerous small sections which are redivided by the next group which follows. The halves of adjacent segments so divided flow together to form fresh masses which are in turn bisected and reformed by the fusion of the divided parts. This process is repeated over and over again and the rhythmical kneading of the food results in a thorough mixture of its constituents with the digestive juices. It also encourages the absorption processes by continually brining the chyme into contact with fresh mucous surfaces; and by the massaging effect of the movements upon the bowel wall, the flow of lymph and blood through the lacteals and capillaries is hastened. The segmenting movements have been observed by Hertz and others in the human intestine by radioscopy but their rhythm was slower—about 8 per minute.

PENDULAR MOVEMENTS

These like the segmenting movements are simple annular constrictions. They travel up and down short lengths of the bowel in a to and fro fashion at a rate of about 5 cm. per second. They have the effect of carrying the chyme alternately from one to the other end of a loop of bowel. Their frequency is from 20 per minute in the duodenum to about 10 per minute in the lower ileum. The pendular movements are not always well marked. They are best seen in the rabbit, though they occur also in other animals and sometimes in man. At times they are very active and appear to throw the food material rapidly and with considerable force from end to end of a small section of the bowel. They constitute another factor contributing to the thorough mixing of the food; they have no direct effect upon the movement of food through the digestive tube, but exert a purely local churning or "shaker-like" action.

MOVEMENTS OF THE INTESTINAL VILLI

If the intestinal mucosa of a living animal be exposed and examined under the low power of the microscope the villi can be seen to be in constant motion—swaying from side to side, shortening and elongating alternately, or lashing to and fro, either singly or in groups. The movements are due apparently to rhythmical contractions of smooth muscle fibers situated within the villi. By constantly stirring the fluids which bathe the surfaces of the villi, these movements undoubtedly

aid the digestive and absorptive processes (see also pp 453 and 504).

THE METABOLIC GRADIENT THEORY OF ALVAREZ

Alvarez believes that the fundamental factor determining the polarity of intestinal peristalsis is the gradual diminution in the metabolic activity of the intestinal muscle that occurs from the duodenum downwards. A parallelism was found between the magnitude of the energy exchanges of the bowel at different levels and its muscular activity. Rhythmicity, irritability and force of contraction and tone are graded from above downwards, being high in the duodenum and low in the ileum. The length of the latent period of the muscle also shows an increase as the intestinal tract is descended. The carbon dioxide production and oxygen consumption exhibited a corresponding decrease from the duodenum to the lower reaches of the intestine. The frequency of the rhythmical segmenting contractions (p. 497) is 17 per minute in the duodenum but only 10 in the lower ileum. Warming a strip of ileum raises its metabolism; its rate of beat is increased to equal that of the duodenum while the latent period is shortened. The decline in the metabolic rate from duodenum to ileum is spoken of by Alvarez as the *metabolic gradient*; to it are ascribed the progressive diminution of the other physiological activities of the muscle. Upon the difference between the intensities of the latter at any two levels of the digestive tube, the direction and swiftness of the peristaltic wave are supposed to depend. Alvarez suggests in illustration of his conception, water flowing between two regions of unequal pressures. When the gradient has the normal slope, peristalsis is active and downward in direction. An inflammatory or irritative lesion, however, according to this observer, may raise the metabolic rate at a certain point so that it approaches, equals, or rises above that at a point nearer the pylorus. In such a circumstance the gradient would become reduced, annulled or even reversed. Sluggish peristalsis, stasis or antiperistalsis, respectively would result. Reversal of the gradient and the production of antiperistalsis as the result of mechanical blockage of the lumen, or injury and inflammation of a region of the bowel are advanced to explain the passage of fecal material into the stomach in intestinal obstruction and paralytic ileus.

The theory is interesting and suggestive. It accords with many experimental and clinical observations, but cannot be said to have been established.

THE ILEO-COLIC VALVE (VALVULA COLI)

This structure when competent permits the passage of the contents of the small intestine at intervals into the cecum, but hinders the return of the material into the ileum. Its ability to do this depends, according to one view, not upon any mechanical valve-like device, but upon the con-

traction of the circular fibers of the gut which are thickened in this region to form a sphincter guard for the ileo-cecal orifice. Most observers agree, however, that the competency of the ileo-colic valve is actually due to a valve-like construction. The ileum enters the cecum obliquely and in doing so invaginates the cecal wall; this alone would tend toward a valve-like action. The valve proper is formed as follows. As the lower end of the ileum enters the cecum, the invaginated portion of the cecal wall forms two transverse folds or lips, one above the other below the ileo colic orifice. The lips fuse laterally to produce a fold on either side of the orifice (*the frenula coli*) which are continued around the interior of the

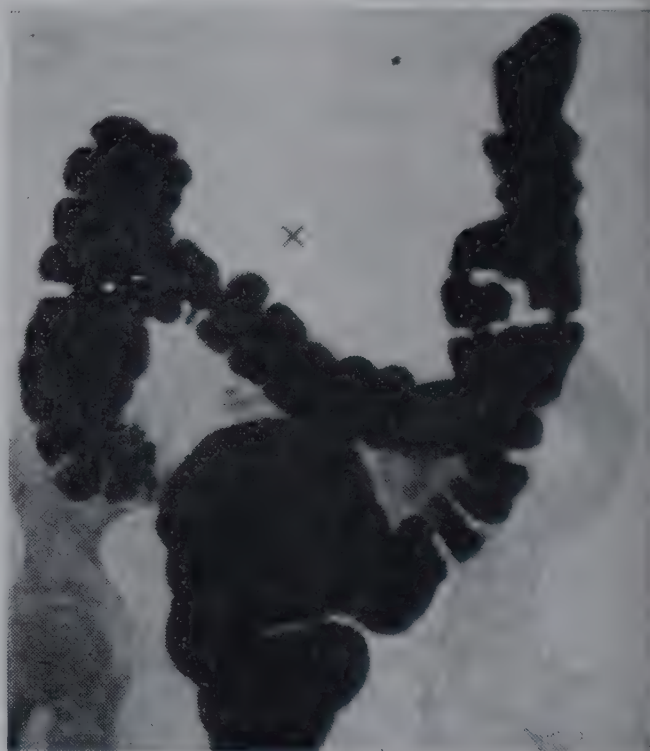


FIG. 208. X-ray photograph of normal large bowel completely filled. (After Barclay.)

cecum. As the cecum distends the frenula are stretched and pulling upon the lips from either side draw them firmly together. Thus the valve can withstand a high pressure in the cecum but yields to a low pressure from above. Material introduced by enema may in some instances pass through the sphincter into the ileum. Such incompetence may permit the enema fluid to reach the duodenum. The ileo-colic opening has been observed in man through a cecal fistula. It appears as an oval or round opening from 2 to 3 cm. in diameter situated in the center of a small papilla. When contracted the sphincter was found to offer considerable resistance to the passage of the finger. While digestion was in progress the papilla was observed to flush, its color altering from a pale pink to a vivid red. The sphincter opened rhyth-

mically at frequent intervals and allowed a jet of fluid to escape into the cecum. Emotional excitement or the swallowing of food increased the frequency of the ejections. During fasting nothing passed through for long periods, but in from $\frac{1}{2}$ to 4 minutes after food was taken into the mouth, fluid appeared in gushes of about 15 cc. every half minute or so.

The functions of the sphincter appear to be (a) to prevent the contents of the ileum from passing into the cecum before the digestive processes are complete (see also antiperistalsis in ileum, p. 496), and, (b) to act as a barrier which prevents the bacteria-laden contents of the large bowel from contaminating the small intestine.

THE MOVEMENTS OF THE LARGE INTESTINE

The contents of the ileum after passing through the ileo-colic orifice collect in the blind end of the cecum. In the human cecum little or no movement can be seen, as a rule, yet the material passes slowly into the ascending colon. This is due in part to filling of the cecum and passive overflowing but in many instances the material appears in the ascending colon *before* the former becomes filled. The forces bringing this about are not known. Todd describes slow changes in the shape of the cecum but thinks such a movement inadequate for the propulsion of its contents. Barclay remarks upon the absence of activity in man which, as he expresses it, presents a picture of "still life." In animals constricting rings may be seen passing over the cecum driving material against its blind end. These have the effect of churning the contents. Such antiperistalsis though not seen normally in the human cecum may, according to Todd, appear when the colon beyond is in a spastic state.

The rest of the human large intestine as revealed by radioscopy is usually free from antiperistaltic, segmenting or pendular movements; and peristalsis is absent or ill-defined. Some hours after a meal the shadow cast by the ascending, transverse and descending colons has usually a segmented appearance—a number of short sections strung together (fig. 208). This appearance is caused by the haustra or sacculations in the bowel wall. Todd describes slow weak peristaltic movements and alternate shortenings and elongations—concertina-like action—in the transverse colon.

MASS PERISTALSIS

This is a movement first described by Holtz-knecht which occurs from time to time in the

colon and sweeps the contents *en masse* for considerable distances along the bowel. The movement is analogous to the peristaltic rush already described as occurring in the small intestine. The mass movement in the colon of which the subject is quite unaware occurs only at long intervals, probably not oftener than two or three times in twenty-four hours. It is frequently preceded by the corresponding movement in the small intestine. It may occur almost immediately after the entrance of food into the stomach—*gastro-colic reflex*. The desire to stool so commonly experienced after breakfast is the result of this reflex; fecal material is forced into the rectum and the defecation reflex initiated (p. 503). Mass peristalsis in the colon may also be induced by purely psychic influences—the taste, smell or thought of food or some disturbing emotion. Alvarez cites an instance of a subject with an incompetent anal sphincter in whom a bowel movement could be precipitated by the mention of savory food.

The movement usually starts in the region of the hepatic flexure. The haustral markings suddenly disappear, the bowel appearing radiologically as a solid unsegmented column. A strong and rapid peristaltic wave then travels over the transverse and descending colons carrying all before it. The haustral markings then reappear (fig. 209). The contents of the more proximal portion of the colon are thus transferred to the pelvic colon which becomes filled from below upwards. The pelvic colon serves as a storehouse for the feces; it is evacuated through the rectum and anal canal by the act of defecation. The descending colon is usually empty except during the time that the feces are being transferred by a mass movement. Feces after they have filled the pelvic colon may, however, extend upward into the descending colon, and may even reach the splenic flexure. Except preceding and during the act of defecation the rectum also is normally empty.

DEFECATION

The act is brought about by the passage of fecal material past the resistance of the pelvi-rectal junction. According to some observers a definite thickening of the circular fibers of the colon (pelvi-rectal sphincter) exists in this situation. The entrance of the feces into the rectum may result from a mass movement already described or simply from overloading of the pelvic colon and the gradual pushing of its contents downward. The fecal masses fill and distend the rectum, and,

when the intra-rectal pressure reaches to between 40 and 50 mm. Hg, the defecation reflex occurs. The reflex consists of a strong peristaltic contraction of the colon, accompanied by shortening of its longitudinal fibers which are disposed in three bands—*taeniae coli*—on its anterior, inner and posterior aspects. The tenia obtain fixed points for their contraction indirectly from the coccyx, through the recto-coccygeus muscles. The latter arise from the coccygeal vertebrae and blend at the lower part of the rectum with the longitudinal fibers of bowel which in this situation have become

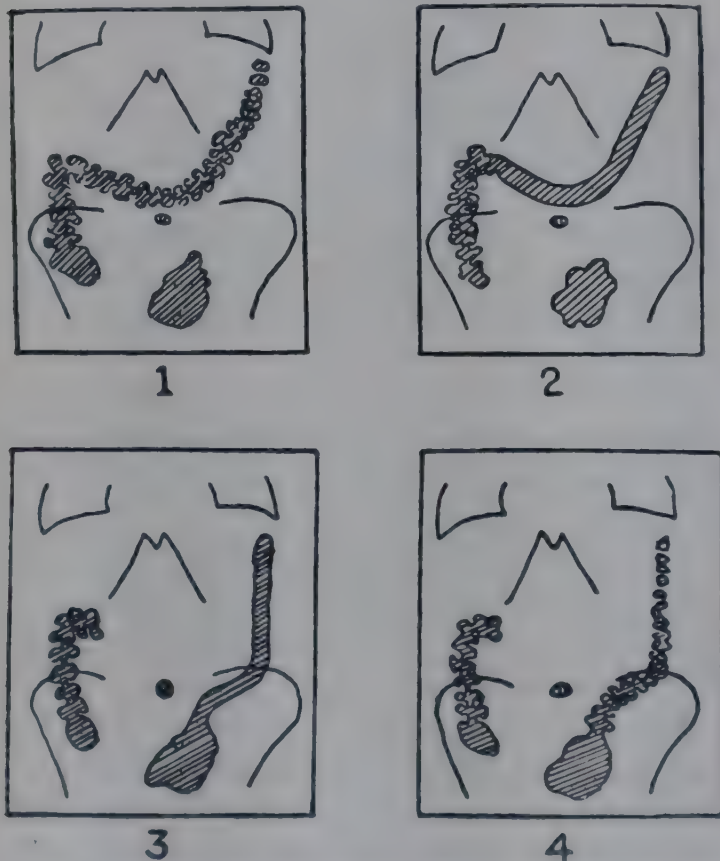


FIG. 209. Holzknicht's diagrams of the happenings during a mass movement of the large intestine. 1, distribution of the food before any change was noted; 2, the haustral segmentation in the transverse colon has disappeared; 3, the whole colon beyond the hepatic flexure passes on suddenly; 4, it is again a picture of "still life" a few seconds later and the haustral segmentation has returned. (After Barclay.)

spread out to form a continuous sheathing for the rectum and anal canal. The contraction of the longitudinal fibers and consequent shortening of the bowel combined with the simultaneous downward progress of the peristaltic wave, and a coördinate relaxation of the anal sphincters, effects the evacuation of the feces. Hurst made observations upon human subjects by means of the X-rays and found that the evacuation of the colon extended as far or even beyond the splenic flexure. The movements of the bowel wall itself are accompanied and assisted by the contraction of voluntary muscles. The diaphragm

descends to its extreme inspiratory position and is held there, the glottis being kept closed during the straining efforts which follow. The abdominal muscles contract powerfully and the intra-abdominal pressure rises. The descent of the diaphragm, as Hurst has shown, causes marked depression of the ascending and transverse colons and of the splenic flexure. The compression of the ascending colon against the nearly stationary cecum forces the former into an almost globular form. The pressure in the rectum, which in an individual in the erect posture amounts at ordinary times to about 20 mm. of mercury, rises to from 100 to 200 mm. during the straining efforts. The pelvic floor is supported against the elevated intra-abdominal pressure by the contractions of the levatores ani, the transverse perinaei and coccygeus muscles. The levatores ani, which pass from the origins downwards on either side of the rectum and anal canal have some of their fibers inserted into the walls of these portions of the bowel and into the fibrous tissue in the neighborhood. By their contraction the anus is drawn upwards over the fecal mass. They also prevent prolapse of the rectum and anal canal, and by constricting the walls of the latter, at the termination of the act effect the expulsion of any material still remaining. The levatores ani serve also to reinforce the sphincters against the action of strong peristaltic waves and so enable the individual, when necessary, voluntarily to resist the evacuating reflex (see also p. 503)

The rate of progress of a barium meal through the human intestinal tract

The time required for the first part of a barium meal (semi-fluid) to pass from the stomach to the pelvic colon varies in different individuals. The usual time is from 12 to 14 hours. The material commences to leave the stomach almost immediately after it has been swallowed; it moves steadily and at a fairly rapid rate through the duodenum and very rapidly through the jejunum. Its progress through the ileum becomes progressively slower as the ileocecal opening is approached and in the lower part of the ileum the material tends to accumulate before it is passed into the cecum. It commences to enter the latter in about 2½ hours on the average. In 4 hours or so the material arrives at the hepatic flexure, and in about 6 hours at the splenic flexure.

Evacuation occurs at variable times after the material has commenced to collect in the pelvic colon but occurs usually in from 16 to 24 hours after the meal has entered the stomach. The first parts of the meal appear in the stools about 24 hours after the food has

entered the stomach and the last tracers in from 36 to 48 hours.

Many factors influence the rate of progress of food along the intestine—(a) The chemical and physical characters of the food. (b) Individual variations in the activity of the intestinal musculature, or in the absorptive function of the colon, and consequently, in the consistency of its contents. (c) The state of fullness of the alimentary tract. After a fast or after the bowels have been cleared by a cathartic the intestinal contents move more rapidly but the time elapsing before it is evacuated may appear to be longer than usual, since the pelvic colon takes time to refill. (d) Muscular exercise increases the rate of movement. (e) Emotional states also tend to increase intestinal activity.

THE ACTIONS OF CERTAIN SUBSTANCES UPON INTESTINAL MOTILITY. Fats, through the production of glycerine and soaps, stimulate the movements of the small bowel; sugars are also excitatory. Acetylcholine and pilocarpine or eserine, given intravenously, are powerfully stimulant. Pituitrin is also excitatory whereas adrenaline is inhibitory.

Atropine reduces the tone of the musculature of the small and large bowel and relieves intestinal spasm. The phasic contractions of the small bowel are also usually decreased in amplitude but sometimes appear to be increased, in any event the propulsive force of the contractions are diminished, so that the progress of material along the intestinal lumen is slowed. The movements of the large bowel, especially of the distal colon, are depressed. Morphine increases intestinal tone; the rhythmical movements (segmenting and pendular) are increased in frequency, but reduced in amplitude. The propulsive movements are profoundly depressed or abolished; constipation results.

THE NEURO-MUSCULAR MECHANISMS GOVERNING THE MOVEMENTS OF THE INTESTINAL TRACT

INNERVATION OF THE SMALL INTESTINE

The wall of the small bowel is composed of an outer longitudinal and an inner circular coat. The latter is considerably thicker than the former. According to Carey both coats are arranged in a spiral fashion. Between the two muscular sheets the *myenteric plexus* (Auerbach's) is situated. The *plexus of Meissner* lies in the submucosa. These two plexuses are connected with one another by nerve filaments which pass between the circular muscular fibers. Auerbach's plexus contains numerous ganglion cells; which are scarce in Meissner's plexus.

The rhythmical contractions—*segmenting* and *pendular*—are myogenic, that is, they are dependent solely upon the rhythmical property of the intestinal muscle itself. They are not abol-

ished by such nerve poisons as cocaine and nicotine. A segment of excised intestine beats rhythmically when immersed in a 1 to 4000 cocaine solution. Furthermore, the contractions of the circular coat of the bowel have been shown by Gunn and Underhill and by Alvarez and Mahoney to continue after it has been stripped from the longitudinal layer, and from the submucosa as well; all ganglion cells are in this way removed. (See also Gasser, and Thomas and Kuntz.)

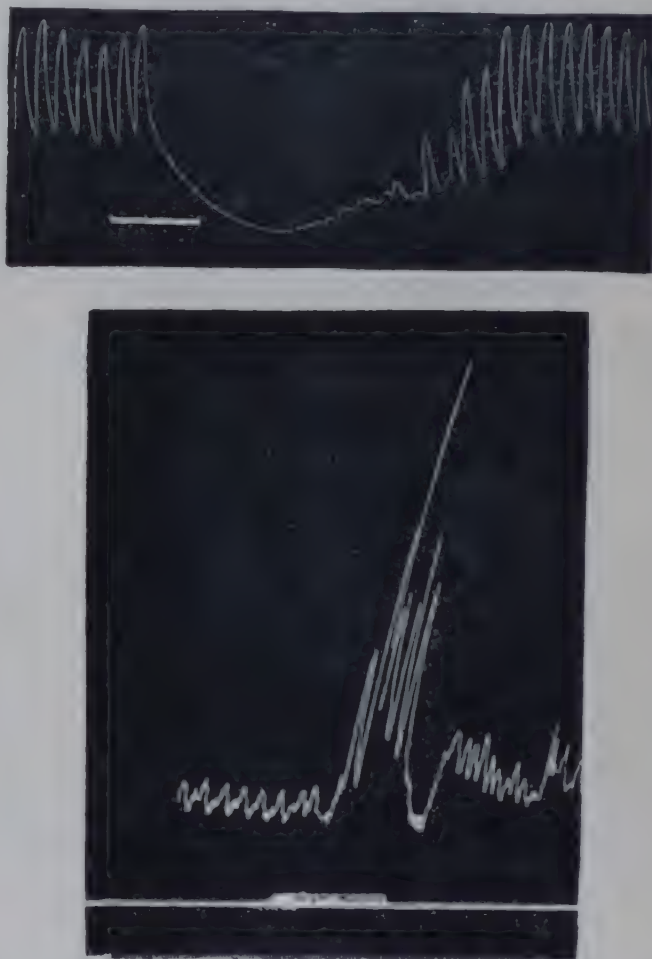


FIG. 210. Upper, shows the inhibitory effect of splanchnic stimulation upon the movements of the small intestine; the heavy white line indicates the time during which the stimulus was applied (after Starling). Lower, shows effect upon intestinal motility of stimulating vagus nerves. (After Thomas and Kuntz.)

The peristaltic contractions, on the contrary, are dependent upon the intrinsic nerve plexuses. But though carried out through local reflexes in the bowel wall (myenteric reflexes of Cannon) they are readily influenced through the extrinsic nerves—the *vagus* and *sympathetic*. It was shown by Bayliss and Starling that section of both these sets of nerves does not abolish the peristaltic movements, whereas the application of cocaine to the bowel wall does. The *vagus*, whose terminals connect with ganglion cells in Auerbach's plexus, augments the movements. The *sympathetic* is inhibitory (fig. 210). The sympathetic fibers pass mainly in the lesser splanchnic nerve

to the lower part of the celiac ganglion and to the superior mesenteric ganglion (fig. 205); from these ganglia the impulses are relayed to the bowel. The postganglionic fibers pass without interruption through the plexuses of the bowel wall to end in direct relation with the muscle cells. The extrinsic nerves also influence the tone of the intestine, the vagus increasing, the sympathetic diminishing this property. The sympathetic exerts a continuous inhibitory action upon the bowel movements which are therefore augmented after section of the sympathetic fibers. It has also been shown by Campbell and Markowitz that spinal anesthesia which temporarily paralyzes the thoraco-lumbar outflow removes the reflex inhibition of the intestine induced in dogs by peritoneal irritation (intraperitoneal injection of tincture of iodine). The vagus on the other hand does not appear to exert any continuous augmentor effect upon intestinal motility, for section of these nerves does not affect the movements.

INNERVATION OF THE COLON

In the cecum and the rest of the colon the fibers of the outer muscular coat are gathered into three longitudinal bands—the *taeniae coli*—which, being shorter than the underlying layer, draw the bowel into the tucks and pockets known as haustra. The circular coat is thickened between the latter. The intrinsic nerves (plexuses) of the colon have a distribution similar to that of the small intestine.

The extrinsic nerves

For a variable distance from its commencement the large intestine is supplied with motor fibers through the vagus. The vagal innervation terminates usually within the first half or third of the transverse colon. The rest of the colon, including the rectum, receives its motor innervation through the pelvic nerves (*nervi erigentes*, p. 942) from the 2nd, 3rd and 4th sacral segments. The pelvic nerves are cholinergic.

Inhibitory fibers to the entire colon are derived from the *sympathetic*. They arise from the lumbar segments of the cord and reach the proximal part of the colon (cecum, ascending and transverse colons) through the inferior mesenteric plexus (p. 940). The fibers to the distal colon (descending, iliac and pelvic colons and rectum) arise from the 2nd and 3rd lumbar segments. They pass via the lumbar splanchnics to the inferior mesenteric ganglion and thence to the bowel by (a) a number of short strands called

the *lumbar-colonic nerves* (also known as *inferior mesenteric nerves*) and (b) the *hypogastric (presacral) nerve*. The lumbar-colonic nerves are the axons of cells situated in the inferior mesenteric ganglion.¹ The fibers entering into the formation of the hypogastric nerve pass for the most part without interruption through the lumbar ganglion. Their cell stations are situated in the hypogastric ganglion. The postganglionic fibers pass through the pelvic plexus to the bowel (fig. 205, 211). The hypogastric nerves, and probably the lumbar colonic nerves as well, are adrenergic.

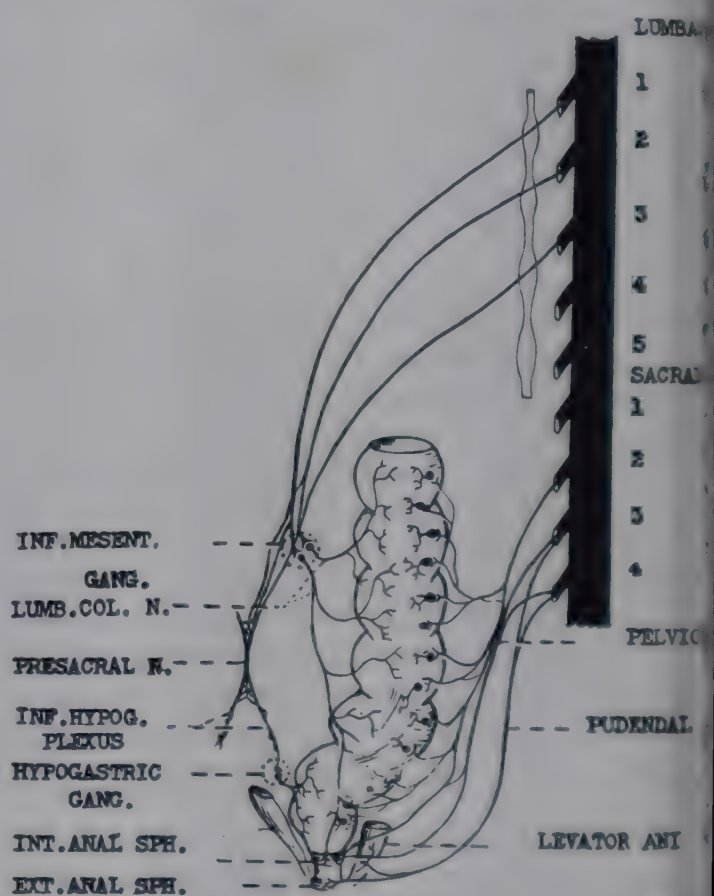


FIG. 211. Diagram of the innervation of the distal colon.

Stimulation of the lumbar-colonic nerves causes relaxation of the distal colon. Learmonth and Markowitz showed that these nerves exert a constant inhibitory action since increased color activity follows their section. Garrey found that though in the decerebrate cat the distal colon is inactive when its sympathetic supply is intact, division of the lumbar-colonic nerves causes rhythmic activity and a marked increase in tone. The hypogastric nerve appears to exert a minor inhibitory influence upon the colon since its division causes only a slight increase in the activity of the bowel. Paralyzing the lumbar outflow with a spinal anesthetic has an effect similar to that

¹ According to Learmonth there can rarely be found in man, a definite structure to which this name can be applied.

nerve section.² The inhibitory impulses of the colon arise apparently within the lumbar cord, for if this region has been isolated previously from higher centers by spinal transection the full augmentor effect upon the colon of sectioning the colonic nerves is obtained.

Section of the *pelvic nerves* (sympathetic innervation intact) relaxes the wall of the distal colon and the animal subsequently experiences difficulty in emptying the bowel. The effect of section of the pelvic nerves upon the tone of the colon is particularly well shown if the bowel has been previously in a hypertonic state as a result of division of the sympathetic supply. Section of the cord above the sacral segments also causes relaxation which indicates that the constant augmentor effect is due to impulses arising in higher centers. A subsidiary augmentor center apparently exists, however, in the sacral cord, for cutting the pelvic nerves some time after spinal transection causes colonic relaxation. That is, the sacral segments acquired control during the time which had elapsed after their isolation from higher centers.

INNERVATION OF THE SPHINCTERS

The sphincters of the bowel—ileo-colic, and the internal and external anal sphincters—exemplify the principal of reciprocal innervation, or what Meltzer termed when speaking of muscular tubes, "contrary innervation." For instance, the motor nerve to the *ileo-colic* sphincter is the same as that which causes inhibition of the bowel wall, namely, the sympathetic. Stimulation of this nerve will in consequence produce a dual effect, contraction of the sphincter and inhibition of the wall of the ileum. In this way the passage of fluid into the cecum is restrained. Logically we should expect the vagus to have an inhibitory effect upon the ileo-colic sphincter, but this action has never been demonstrated, and so far as is known the vagus is without any effect upon the sphincter.

The *internal anal sphincter* is also innervated in a fashion contrary to that of the rest of the large bowel. The pelvic is the inhibitory nerve, while the sympathetic is motor. The sympathetic fibers are conveyed via the lumbar-colonic and hypogastric nerves. Stimulation of parasympathetic fibers will therefore induce evacuation of the bowel by excitation of the bowel wall and relaxation of the sphincter. Stimulation of the

sympathetics on the other hand inhibit intestinal activity and increase the tone of the sphincter; the act of defecation will be restrained. The *external anal sphincter* is composed of striated muscle; it is kept tonically contracted and is under voluntary control. It is said not to atrophy when its nerve supply (derived through the 4th sacral nerve and the perineal branch of the pudendal nerve) is cut, but to recover its tone to a large extent after the operation. Its contraction, with that of the levator ani and other perineal muscles, is an important factor in opposing defecation. Afferent impulses arising in these muscles during their contraction are said to reflexly inhibit the bowel movements.

THE INNERVATION OF THE MOVEMENT OF DEFECATION

The defecation reflex is governed by a medullary center and a subsidiary center in the cord. The existence of the latter is evident in nervous diseases associated with complete functional or anatomical division of the cord above the lumbosacral region, when evacuation is effected automatically and in an almost normal manner. Also in animals after complete transection of the cord, though there is loss of control over the bowel movements and incontinence of feces for a time, the spinal center subsequently assumes control and automatically evacuates the bowel at regular intervals.

The *spinal center* is situated in the second, third and fourth sacral segments, but the destruction of this region in animals is not necessarily followed by complete and permanent fecal incontinence, for the rectum like the bladder (p. 415) is capable of controlling evacuation through its intrinsic nervous mechanisms. Also in involvement of the sacral segments of cord in man there sometimes may be almost perfect automatic control of the rectum and anal sphincter.

The *medullary center* is situated in the floor of the fourth ventricle not far from the vomiting and respiratory centers; Hatcher has shown that a stimulus to defecation will inhibit vomiting and certain emetic drugs (picrotoxin) applied to the vomiting center cause defecation. Hatcher and Weiss found areas in the medulla which controlled the tone of the sphincters. The well known fact that stimulation of the anal sphincter by forcible dilatation is an effective means of stimulating respiration, suggests a close relationship between the respiratory and defecation centers.

² It is likely that the center for the sacral outflow is also paralyzed by the anesthetic but that the bowel movements are then controlled by the intrinsic plexuses.

The reflex as mentioned on page 499 is initiated under normal circumstances by the passage of feces into the rectum. The latter, however, soon adjusts its capacity to the bulk of the feces (postural tone) the pressure stimulus being then abolished. The rectum may therefore become unresponsive³ if defecation is voluntarily prevented. The afferent fibers conveying impulses from the rectum travel mainly if not entirely with the efferents of the pelvic nerve and enter the cord by the posterior roots of the sacral nerves. Afferent fibers supplying the anal canal probably travel in the pudendal nerves. Division of the main afferent paths abolishes the defecation reflex since no impulses can reach the center. There is retention of feces for a time, but as mentioned above the local nervous mechanisms of the bowel wall later assume control.

THE REACTION OF THE INTESTINAL CONTENTS

The reaction of the contents of the duodenum vary considerably in accordance with the acidity of the chyme entering from the stomach and with the volume of the alkaline fluids—especially of the pancreatic juice. The proportion of acid and alkaline fluids varies in turn with the stage of digestion and the type of food, meat tending to increase the acidity of the chyme. In the dog the pH of the duodenal contents may be anywhere from 4.6 to 7.6; the usual value is about 6.⁴ In the human subject, the type of food and differences in the secretory activity of the gastric glands cause considerable individual variations in the reaction of the duodenal contents; in subjects of subacidity or hyperacidity (p. 442), for example, the reaction tends to be more alkaline or more acid, respectively. Samples of human duodenal contents, obtained by duodenal tube, show in most cases a pH between 5 and 6, average about 5.5. In subjects of duodenal ulcer, the pH of the contents of the duodenal bulb during fasting is about 4. Determinations upon healthy animals (rats and dogs) indicate that the contents of the entire small intestine below the duodenum are almost always definitely acid in reaction. From observations made upon patients with intestinal fistulae, this is most probably true also of the human intestine. The acidity of the small intestine (except in its upper part) is due to organic acids resulting from the action of fermentative types of bacteria (p. 510). In rats there

occurs a progressive rise in pH from the upper to the lower levels of the small intestine. The average pH of the contents of the former is around 6 and of the latter about 6.8. The pH falls slightly in the cecum but rises again in the colon. The feces have a faintly acid, neutral or a faintly alkaline reaction (6.9 to 7.2). In rachitic animals the pH of the intestinal tract and the feces is higher than that of normals. The administration of cod-liver oil or exposure to sunshine restores the reaction to the normal level. (Zucker and Matner)

ABSORPTION FROM THE GASTRO-INTESTINAL TRACT

Alcohol is absorbed from the stomach, but water, glucose and other materials in only negligible amounts pass through the gastric mucosa. The absorption of food materials is practically confined to the small intestine. Absorption from the colon is restricted mainly to water and inorganic salts. Glucose solution (10 per cent) introduced by enema may be absorbed in considerable amounts but the absorption of proteins and fats is for practical purposes (rectal feeding) unimportant. The absorption of the different food materials from the small intestine is considered in the respective sections dealing with the metabolism.

The villi are the absorbing units of the small intestine. Each of these minute finger-like processes is covered by a layer of columnar epithelium, and contains a capillary loop and lymph vessel (lacteal), a small amount of connective tissue and strands of smooth muscle. There are some 5,000,000 villi in the human intestine which provide a total absorbing surface of some 10 square meters (fig. 196, p. 453). Amino-acids and glucose are absorbed into the capillaries; about 60 per cent of the digested fat can be recovered from the thoracic duct; the remainder is absorbed apparently into the portal blood.

Attempts have been made to explain intestinal absorption by known physico-chemical laws. The factors of a physico-chemical nature whereby absorption might conceivably be brought about are: (a) Differences in concentrations and therefore of the diffusion pressures between crystalloids in the blood and in the intestinal lumen. (b) The hydrostatic pressure within the intestine created by the intestinal movements, which would tend to drive water and dissolved substances across the epithelial boundary. Hamburger found that absorption varied directly with the intraluminal intestinal pressure, and Wells has shown that the absorption of water from isotonic sodium chloride

³ This was well shown in the human subject by Hurst. When the rectum was inflated the call to defecate became urgent, but the intrarectal pressure fell again within half a minute or so, as a result of the adaptation of the rectal walls to the distending force, and the sensation passed off. Rapid re-inflation caused the sensation to return and then pass away again as the pressure fell.

⁴ It will be noted that this is not the optimum pH for the action of the pancreatic enzymes.

ride solutions ceased when the intra-intestinal pressure was reduced to from 8 to 26 cm. below that of the atmosphere, but that the absorption rate increased in proportion to the increase in intra-intestinal pressure above this level. (c) The osmotic pressure of the plasma proteins in excess of the hydrostatic pressure of the capillary blood pressure was suggested by Starling as an important factor in attracting water and crystalloids into the blood stream. It has been estimated that the colloid osmotic pressure is some two or three times greater than the blood pressure in the capillaries of the villus. (d) Hober suggests that electrical forces in the nature of cataphoresis (the transfer of a solute across a membrane from anode to cathode) play an important rôle.

Though some or all of the factors enumerated above probably play a part in the absorption process, there are several observations which cannot be explained upon a purely physico-chemical basis, some specific "vital" activity must be attributed to the epithelial cells of the villi. For example, materials such as glucose and sodium chloride are absorbed from hypotonic solutions (i.e., solutions containing the material in lower concentration than it exists in the plasma). Also, as shown by Cori, the absorption of glucose from the intestine may continue at a practically constant rate for hours though its concentration diminishes progressively; on the other hand, the absorption of a material, such as glucose, can not be increased by simply reducing its concentration in the plasma. Such facts cannot be explained by the laws of diffusion. Moreover, Hewitt has shown that when glucose, galactose and fructose in equivalent concentrations are placed in an intestinal loop the relative absorption rates are glucose > galactose > fructose. After destruction of the epithelial lining all three sugars are absorbed at the same rate. Macleod and associates found that glucose was absorbed more rapidly from a surviving intestinal segment than the foreign sugars xylose, mannose and arabinose. This preferential absorption of glucose disappeared when the temperature of the segment was lowered to 0°C. The sugars then passed through the intestinal wall in accordance with their diffusion rates through a dead membrane—xylose with the smaller molecule diffusing more rapidly than glucose.

That the epithelial covering of the villus is not merely a passive membrane, but performs a specific function which entails the expenditure of energy, is also indicated by the experiment of Bro-

die, Cullis and Halliburton. They observed an increase of over 150 per cent in blood flow, oxygen consumption and carbon dioxide production during the absorption of salt solutions of different concentrations. They concluded that a specific function of the epithelial lining, rather than contractions of the wall of the intestine was responsible for the increased metabolism. In the more recent experiments of Van Liere and his colleagues, it was found that oxygen lack does not impair the absorption of all substances alike. Anoxic anoxia to a degree compatible with life does not reduce the absorption of glucose and actually increases the absorption of glycine. Nor is the absorption of sodium sulphate reduced by anoxia. A phosphorylation process rather than an oxidative one is probably concerned in the absorption of glucose, which would account for its being unaffected by anoxia. Anoxic anoxia definitely depresses the absorption of sodium chloride, but anoxia produced by hemorrhage actually increases absorption of isotonic salt solution.

Any consideration of intestinal absorption recalls the process of selective reabsorption by the cells of the renal tubules and suggests that similar factors are concerned. That the cells of the intestinal mucosa perform chemical work, as in the absorption of fat (p. 599) is accepted. Reabsorption of water and dissolved substances from the glomerular filtrate is, one might say, a process of reverse secretion—from tubular lumen to blood. The laws of diffusion are just as inadequate to account for the absorption from the intestinal lumen as they are to explain the reabsorption process in the kidney.

THE FORMATION OF FECES

The contents of the ileum have an almost liquid consistency. The quantity of fluid material passing through the ileo-colic valve in 24 hours is in the neighborhood of 400 grams. The feces evacuated during an equivalent length of time is about 150 grams. The fluid is absorbed mainly by the cecum and ascending colon, but also in smaller amounts during the progress of the feces along the transverse and descending colons and during their stay in the pelvic colon. The feces are neutral, slightly acid or slightly alkaline in reaction (p. 504).

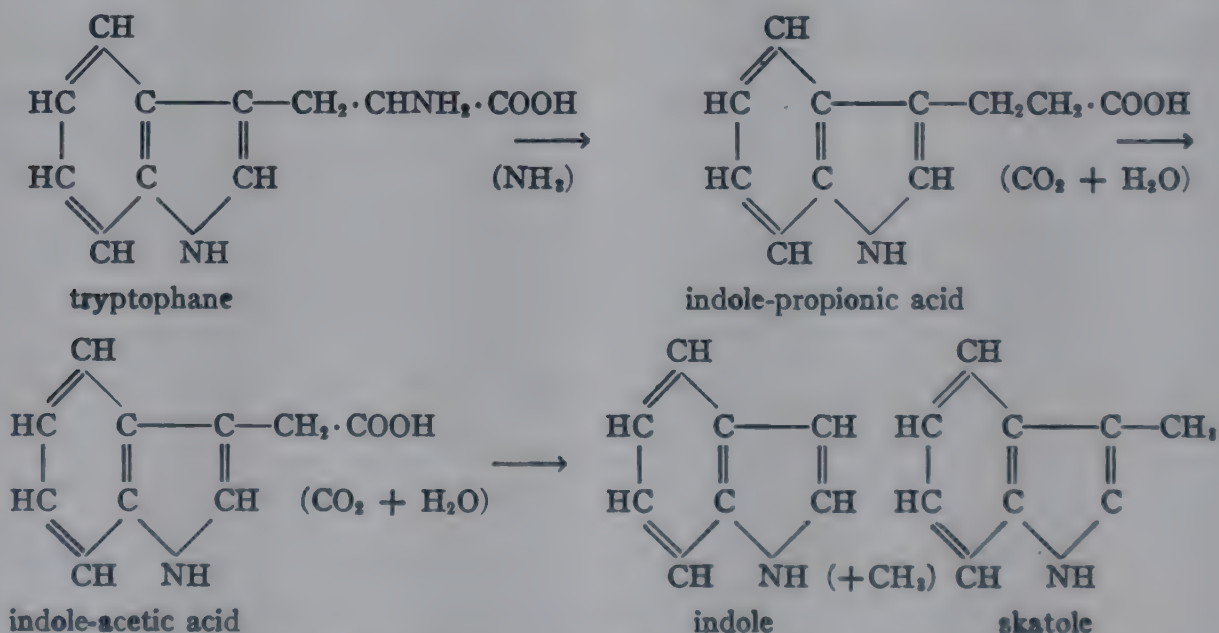
The feces are composed of food residues, bacteria, material secreted through the wall of the intestine and in the bile, leucocytes and desquamated epithelial cells. Food residues constitute a much smaller proportion of the bulk of the feces than

is usually realized. The fat, protein and carbohydrate of the diet is practically all absorbed and if the food be free from indigestible material, especially cellulose, the feces are composed almost entirely of bacteria, secretions, etc. During starvation, for example feces continue to be formed and their composition does not differ materially from that of feces passed after an ample diet. Also, a segment of bowel when isolated from the rest of the intestinal tract becomes after a time packed with a mass of pasty fecal material, which of course must be entirely endogenous. Wide variations in the composition of the diet, if the quantity of cellulose remains unaltered, exert little or no influence upon the composition of the feces. The bulk of the feces is reduced however, during starvation, but the reduction is due to the removal of the stimulating effect of the food upon the secretory activity of the intestine. Indigestible materials, especially cellulose, increase the amount of the feces, not only by adding directly to their bulk, but also through increasing the production of endogenous material.

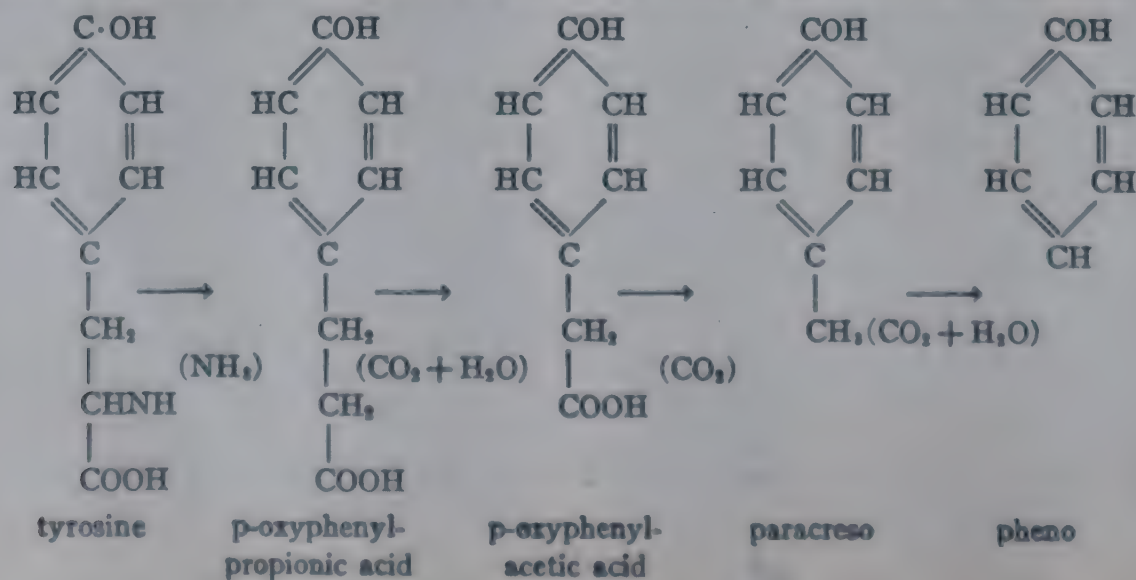
Bacteria constitute ordinarily about 9 per cent

of the total solids of the feces. The nitrogen human feces amounts daily to between 0.5 and gram and, as just mentioned, is largely endogenous. Fecal "fat" is also largely endogenous, continuing to appear in the feces though all fatty material has been excluded from the diet; it differs chemically from ordinary food fat but resembles closely the blood lipids. It consists mainly of lecithin and coprosterol, the latter being derived from cholesterol through the reducing action of bacteria. A certain proportion of the fecal fat is also derived through bacterial action from non-fatty sources. In human feces a part (cholesterol and lecithin) is of biliary origin. Calcium, phosphate, magnesium and other inorganic materials in the feces are also derived mainly from the blood. Fecal iron is mostly exogenous (see p. 59).

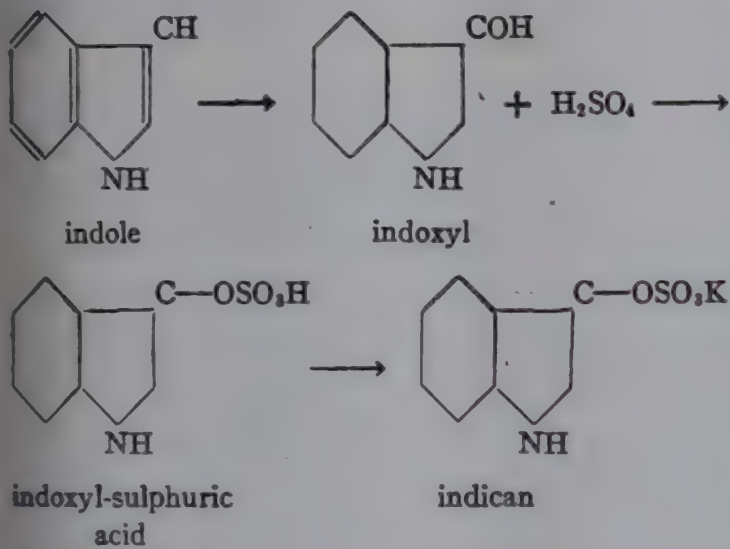
The feces owe their color chiefly to *stercobilinogen* (urobilinogen, p. 460) produced by the bacterial reduction of bile pigment; their odor is due to the presence of aromatic substances, chiefly *indole* and *skatole*, derived from the deamination and decarboxylation of tryptophane by bacterial action in the large intestine (p. 508). Thus



Phenylalanine and tyrosine are converted in a similar manner to paracresol and phenol.



Small quantities of indole, skatole and phenol are absorbed into the blood stream but undergo detoxication in the liver by conjugation with sulphuric acid and potassium or with glycuronic acid. Phenol may undergo conjugation in either of these ways; in the former instance phenol sulphate of potassium is formed, in the latter the corresponding glycuronate results. Indole and skatole after absorption are converted to indoxyl which then for the most part combines with sulphuric acid and potassium to form *indoxyl sulphate of potassium* or *indican*, which is excreted in the urine.



Indole and skatole are also conjugated but in relatively small amounts with glycuronic acid

obstruction, e.g., tumor, adhesive bands, strictures somewhere along the bowel, the chief causes are the following:

(1) *Habit*. The act of defecation can usually be readily inhibited by an effort of the will. The refusal to respond to the sensation aroused by a full rectum and the failure to acquire the habit of clearing the bowels regularly at some definite time each day, e.g., after the first meal, is a common cause of constipation. The rectum becomes tolerant, and adapts itself to the increased fecal bulk. (See footnote, p. 504). As a result, the desire to defecate passes. The retention of feces in the distal colon and rectum leads to the excessive absorption of fluid; the feces therefore become dry and hard and less easily expelled. There may at first be no defect in the musculature or movements of the digestive tract as a whole but the lower segment of the colon as a result of continued overloading becomes sluggish. Atony and thinning of the muscular wall may eventually result. To this type of constipation Hurst has applied *dyschezia* (meaning a difficulty in easing oneself). It is obvious then that properly regulated habits are more likely to correct this condition than the use of purgatives which stimulate peristalsis in an intestinal wall that is, in general, in no need of urging. By purgatives "the whole intestinal tract is teased and pained for the defective action of that part of it which is most remote from their influence."

The dyschezia may be aggravated by other factors. Sometimes the angle at the junction of the pelvic colon and rectum is abnormally acute. On the other hand, spasm (or achalasia) of the circular fibers (sphincter) in this situation may be present which offers considerable obstruction to the passage of feces. Weakness of the muscles of the abdominal wall or of the pelvic floor, e.g., the levator ani, may impair the ability of the lower bowel to evacuate its contents.

(2) A *diet* that leaves too little of the necessary residue for the stimulation of intestinal activity or one which contains too little fluid.

(3) A *colon* which absorbs too readily—the "greedy" or "thrifty" colon as it has been called—and causes undue condensation of the intestinal contents.

(4) *Hypertonic state of the musculature of the colon* is a cause of what is termed *spastic constipation*. Both the transverse and descending colons are sometimes held firmly contracted to form a solid cord which may sometimes be felt through the abdominal wall. At other times only the pelvic

* Chevalier, 1819, quoted by Hurst

1. Epitome
2. pharmacopeia
3. national formulary
4. ~~pharmaceutical~~
4. pharmaceuticals
5. drugs

and descending colons are affected or again the spasm may be confined to the transverse colon. The contracted bowel is the seat of purposeless spasmodic contractions which have little effect in moving the food onward. The spasticity may be reduced by atropine which acts by depressing the parasympathetic influence upon the large intestine. The hypertonic state supposedly may be induced reflexly through impulses arising in diseased pelvic or abdominal viscera, e.g., the gall-bladder, duodenum or appendix. On the other hand, it may be due to influences of a mental nature, overwork, worry or shock, etc. In the constipation of chronic lead poisoning a spastic state of the colon exists.

(5) *Weakness or depressed activity of the musculature of the colon—atonic constipation.* An inherent defect in the neuromuscular mechanism of the bowel is uncommon. Atony of the intestinal musculature may, however, be associated with certain general conditions, e.g., senility, obesity, etc., constitutional diseases or lesions of the central nervous system. The driving force of the intestinal muscle under such circumstances is subnormal. The delay in the movement of the food may be in the small as well as in the large intestine. A hypotonic state of the intestinal musculature may also result from a diet low in vitamin B₁ (p. 642). Rats fed on diets deficient in inorganic salts show loss of tone and depressed motility of the intestinal tract (Robertson and Doyle). The condition is corrected by adding Ca and K to the diet; which suggests that a low intake of these minerals may be a factor in some cases of chronic constipation in the human subject.

The subjective manifestations of constipation are considered elsewhere (see p. 507).

MEGACOLON—HIRSCHSPRUNG'S DISEASE. This is a relatively rare condition appearing in childhood and characterized by obstinate constipation, tremendous dilatation of the colon and hypertrophy of its wall. The condition is due to an abnormality in the innervation of the colon—an imbalance between the activities of the thoracico-lumbar and sacral outflows. Degeneration of the cells of Auerbach's plexus at the pelvi-rectal sphincter has been described (Cameron). This observation of itself would suggest that the cause of the condition is underactivity of the parasympathetic innervation (motor) rather than overactivity of the sympathetic (inhibitory). According to Hurst, and to Gask and Ross, failure of the pelvi-rectal sphincter or of the internal anal sphincter to relax coordinately with contraction of the colonic wall—*achalasia*—is an important element in the pathogenesis of megacolon (see cardiospasm p. 482). The marked hypertrophy of the

bowel wall seen in some cases supports this view. It is most likely, however, that the imbalance between the sympathetic and parasympathetic innervations is not confined to the sphincters but affects the bowel wall as well. This conclusion is borne out by the fact that the dilated and immobile colon shows strong and effective contractions of the bowel after a spinal anesthetic (fig. 212), an effect which also argues strongly against the view that, in most cases at any rate, the parasympathetic is primarily at fault. It seems to indicate, on the contrary, that the motor mechanism is intact but under the influence of an inordinate inhibitory action exerted through the sympathetic. Furthermore the most successful treatment of the condition consists in excision of the lumbar sympathetic ganglia, or section of the hypogastric (presacral) and inferior mesenteric nerves (p. 502).

INTESTINAL INTOXICATION

THE LARGE INTESTINE

Several substances, some intensely toxic in character, are formed in the large intestine as a result of the decomposition of protein by the normal bacterial flora (colon type of organism). Among such putrefactive products are histamine, phenol, cresol, indole, skatole, ethylamine, isoethylamine, tyramine, etc. (p. 506). Choline is also formed as a result of the decomposition of lecithin and choline gives rise to traces of neurine. Some observers, impressed by the powerful actions of these substances when injected into animals, have suggested that their absorption into the general blood stream is responsible for many ills, and particularly for the well-known symptoms of constipation. Metchnikoff arraigned the colon as the body's greatest enemy. Arbuthnot Lane in more recent times inveighed against this cess-pool and recommended its extirpation under certain circumstances. No reliable evidence can, however, be cited to connect any of the toxic products mentioned with the symptoms of disease. Many of them are produced only in mere traces, and even though some, such as indole, are produced in relatively large amounts (60 mg., according to Herter, may be present in 100 grams of feces), toxic doses are prevented from entering the systemic circulation by the barrier offered by the bowel wall and through the detoxicating action of the liver (p. 507). Indole, for example, when given to the human subject by mouth in an amount (1 gram), which is more than would ever be present in the bowel at one time, produces no symptoms; 2 grams causes only some dizziness and a slight headache, while large amounts may be introduced into the colon without ill effect.

slight absorption of indole and skatole under ordinary circumstances is indicated by the fact that though the feces contain considerable amounts of both these substances, the detoxicated product indican (indoxyl sulphate of potassium, p. 507), may be absent from the urine. On the other hand, the ability of the liver to protect the body against these substances is shown by the observation that large amounts of indican are constantly present in the urine of certain individuals, showing that considerable quantities of the putrefactive products are absorbed, yet such persons enjoy good health.

Choline may be given by mouth with impunity; even when relatively large amounts (15 to 20 mg.

Weiss and associates that in the case of the human subject 20 mg. of histamine may be injected per hour without causing a depressor effect; 500 mg. given orally were inert.

According to Alvarez the symptoms of constipation—headache, furred tongue, foul breath, malaise, etc., are of reflex rather than of toxic origin. Afferent impulses set up from the wall of the overloaded rectum appear to be responsible. Distension of the rectum by inert material such as absorbent cotton has been shown to produce almost all the symptoms of constipation. In the dog, packing the rectum in this way causes a rise of some 10 mm. Hg in blood pressure which is maintained until the foreign material is removed.

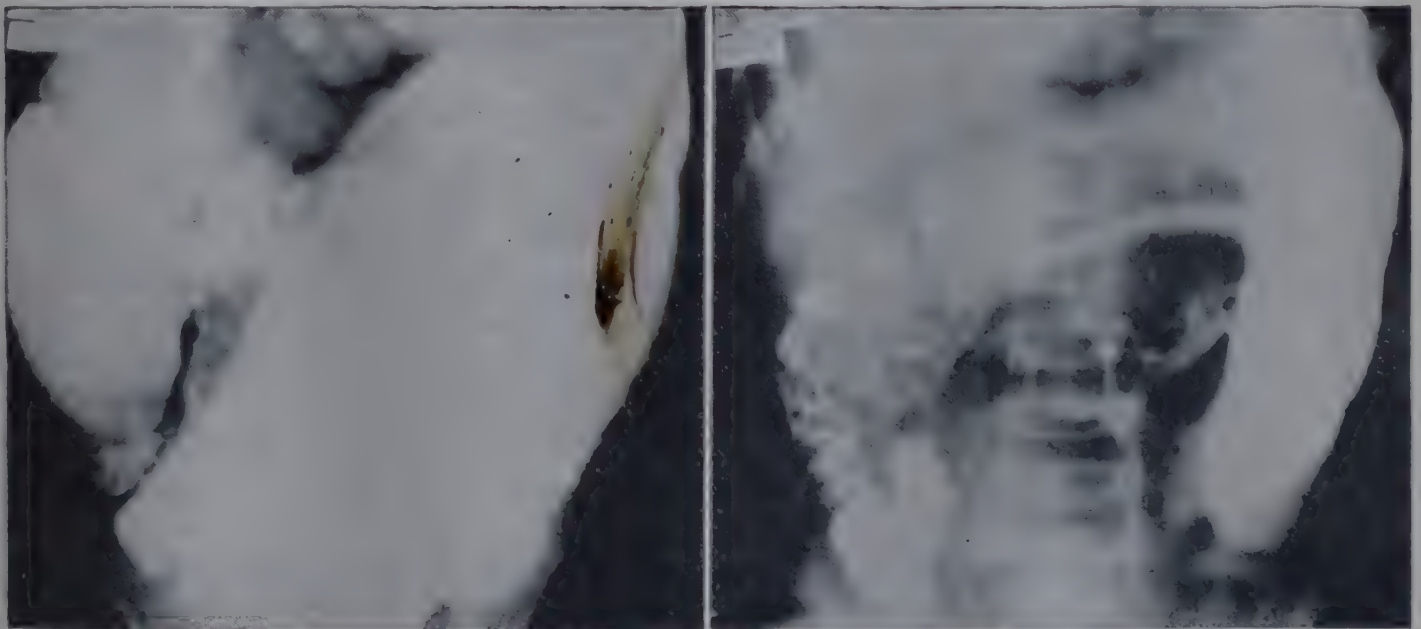


FIG. 212. Megacolon. Motor test with spinal anesthesia. Left, the injection of three and one-half quarts of fluid causes painless distension of abdomen. In horizontal position no spontaneous expulsion after fifteen minutes of effort. Right, fifteen minutes after spinal anesthesia. Note the emptying of the lower sigmoid and most of the ascending colon, also the reduction in diameter of the upper sigmoid. (After Scott and Morton.)

per kilo. in the cat) are given intravenously no toxic effects are produced. Since this substance is rapidly destroyed in the blood stream, large amounts may be injected slowly over a period of time without noticeable effect.

Histamine, another powerful depressor substance was found by Meakins and Harington in minute amounts in the cecum, but only insignificant amounts, they conclude, pass through the intestinal wall. Even after the introduction of large amounts into the *small* bowel only slight absorption was evident. Hanke and Koessler gave the amine by mouth in doses of 100 mg. to guinea-pigs; there were no ill effects, and upon analysis of the intestinal contents 24 hours after the administration of this amount, less than 2 mg. were recovered. The chief protection against the toxic effects of histamine is apparently in the bowel wall itself. It has also been found by

The manifestations of constipation referable to the alimentary tract, namely, the loss of appetite, coated tongue and offensive breath are, according to Alvarez, probably due to small waves of contraction originating in the wall of the loaded bowel and traveling in a reverse direction over the small intestine, stomach and esophagus (p. 480). A strong argument against the symptoms of constipation being due to toxic absorption is the almost immediate relief which follows evacuation of the bowels—it would certainly take some time for the blood to be cleared of the poisonous material. Furthermore, in constipation the feces are relatively dry and hard, conditions much less, rather than more favorable to the absorption of putrefactive products. One should expect, indeed, that the latter would occur more readily during diarrhea. Apart from all the indirect evidence against a toxic element being concerned in constipation,

is the positive fact that many subjects of the disorder, even though this is of a severe grade, do not excrete indican in the urine and, as mentioned above, other individuals who for some unknown reason excrete large quantities remain free from symptoms.

There seems little doubt that toxic products of the bacterial flora of the large intestine are prevented from entering the systemic circulation in amounts that are pathologically significant. The microorganisms themselves may however, leave their normal habitat via the lymphatics and locate in the mesenteric lymph-nodes, or may even enter the general circulation.

THE SMALL INTESTINE

The immunity of the body to autointoxication applies only to the large intestine. The small intestine is not equipped in the same degree to resist the passage of toxic products into the blood stream. Normally, however, the bacterial flora of the small intestine are quite different from those of the large. The microorganisms (e.g., *Bacillus bifidus*) in the former situation have a fermentative not a putrefactive action. Through their action upon carbohydrate, organic acids, acetic butyric and lactic, are produced. The acid reaction of the ileal contents is unfavorable to the growth of the proteolytic bacteria. So long as the supply of carbohydrate material is adequate the microorganisms of the acid-producing type flourish and any of the bacteria of the large intestine which may have invaded the small intestine are unable to gain a foothold. Under certain circumstances, however, especially in infants, this does occur. In young children, in whom the protective power of the small intestine is even less than that of adults a severe type of toxemia results, characterized by vomiting, diarrhea, dehydration, acidosis, fever, emaciation and great prostration.

Some believe that guanidine is the toxic product concerned in certain types of intestinal intoxication in infants. In intestinal disorders associated with the extension into the small intestine of the flora of the large, measures are directed toward encouraging the normal acid-producing type of organism in gaining the upper hand. Carbohydrate is supplied, usually in the form of lactose, which passes farther down the intestinal tract than other sugars before it is absorbed. It has also been common practice to administer cultures of the fermentative type of organism, such as that of sour milk—*Bacillus bulgaricus* (so-called as the result of the writings of Metchnikoff who attributed the health and longevity of the Bul-

garian peasant to his drinking large quantities of sour milk). Today cultures of *Bacillus acidophilus*, one of the normal inhabitants of the small intestine, are usually employed. Ordinary *antiseptics* given with the view of inhibiting bacterial growth exert no appreciable effect, although certain sulphonamides are valuable for their bacteriostatic action.

ACUTE INTESTINAL OBSTRUCTION

Symptoms of intense severity result when the lumen of the small bowel is completely obstructed as a result of constriction by an adhesive band, kinking, twisting or pressure by new growth, intussusception, strangulation by a hernial ring etc. The condition is ushered in by severe cramp-like abdominal pain, vomiting and shock. If the condition is not relieved by operation, reverse peristalsis arises above the point of obstruction, intestinal contents pass into the stomach and the vomiting becomes fecal in character. Later the bowel above the obstruction loses its tone, becoming dilated and filled with intestinal secretion and gas. The loss of fluid in the vomitus and the drainage of large quantities of fluid into the distended bowel leads to a *fall in blood chloride alkalosis* and *dehydration* (p. 17). Other blood changes are a *rise in the non-protein nitrogen* and an *increase in the fibrinogen content*. The former is the result of tissue destruction combined with impairment of renal function. Great prostration occurs, ending in death.

Functional obstruction. The dilated, immobile state of the bowel described above as occurring in the later stages of a mechanical obstruction occurs from other causes and is then referred to as *paralytic* or *adynamic ileus*. The most common cause of paralytic ileus is peritonitis; it may also result from some severe intestinal injury or undue handling and exposure of the bowel during abdominal operations. The distended bowel is incapable of propelling the feces along its lumen that is, obstruction of a functional character exists. When the bowel above a mechanical obstruction has become atonic and dilated, functional obstruction tends to persist after the mechanical block has been relieved by operation. For this reason late operations for the relief of acute intestinal obstruction are attended by very high mortality.

EXPERIMENTAL OBSTRUCTION

When the intestine of an animal is tied across the symptoms which follow are chiefly weakness, prostration and vomiting. The animal shows

little or no evidence that it is suffering pain. The higher in the intestinal tract that the obstruction is made, the more severe are the symptoms, and the shorter is the duration of life after the operation. Following obstruction of the colon the animal may survive for some weeks, whereas after obstruction of the jejunum or duodenum it dies as a rule within five or six days. Reduction in blood volume (anhydremia); fall in blood chloride (see below); increased alkali reserve and non-protein nitrogen of the blood, and a rise in the percentage of fibrinogen occur.

Paralytic ileus may be produced in dogs by the injection of a solution of iodine into the peritoneal cavity. It was shown by Campbell and Markowitz that the intestinal inhibition produced in this way could be abolished by spinal anesthesia which apparently blocked inhibitory impulses reaching the bowel through the splanchnic nerves (p. 502).

A CONSIDERATION OF THE CAUSE OF DEATH IN MECHANICAL OBSTRUCTION

A number of theories have been advanced in recent years in attempts to give an explanation for the symptoms and death in acute mechanical obstruction of the bowel. We may, at the outset, dismiss the possibility that death is simply the result of blockage of the alimentary tract, and the prevention of the passage of food along its lumen. It was shown originally by Stone, Bernheim and Whipple that if a few inches of the bowel were excised, both ends of the segment closed and the continuity of the digestive tract then re-established by an anastomosis of the cut ends of the bowel, death occurred even more rapidly than if the bowel had been obstructed by ligation. The survival time after the closure of such an isolated segment or loop is rarely more than 3 or 4 days and may be only 24 hours.

Toxic theories

A bacterial theory in one or other of its modifications has had its adherents. The toxin of the Welch bacillus has been suspected by some, but little support has been given by recent work to the belief that this or any other bacterial toxin is responsible for the symptoms. Others have thought that a toxic agent derived from the bacterial decomposition of protein within the intestinal lumen was the lethal agent. Histamine, in particular, has been mentioned in this connection. Though the increased excretion of ethereal sulphates (p. 551) which occurs in intestinal obstruction indicates that putrefactive products

are absorbed into the blood stream in larger amounts than usual, all the evidence is against histamine or any other of these substances playing a leading rôle in intestinal obstruction (see also p. 508). It is impossible to consider seriously any bacterial theory of intestinal obstruction, for such theories ignore the fact that the symptoms diminish in intensity, and the survival time is lengthened, the lower in the intestinal tract that the obstruction is produced. Bacterial growth, protein decomposition and histamine concentration on the other hand, are all greater in the lower than in the higher reaches of the intestinal tract.

Whipple and his associates obtained a substance which they believed to be a *proteose* from the mucosa of the obstructed bowel; normal bowel did not yield it. When injected intravenously into normal animals, the material proved to be intensely toxic, producing symptoms similar to those of intestinal obstruction. It was quite innocuous, however, when given by mouth, or when introduced directly into the bowel. These workers, therefore, concluded that death in acute obstruction was due to a toxemia—the absorption of a toxic proteose formed in the mucosa of the obstructed bowel. There has been no confirmation of this theory by more recent work.

The dechlorination and dehydration theory

It was first shown by Hartwell and Hoguet (1912) that obstructed animals which survived for some days showed marked dehydration. Vomiting, it was claimed, was responsible for the reduction in body water; the symptoms of obstruction and death were believed to be the direct consequence of the dehydrated state. They showed, and their observation was confirmed by Haden and Orr and others, that the life of an animal with an obstructed intestine could be prolonged by the subcutaneous or intravenous administration of saline.

That the loss of chloride in the vomitus may cause a profound fall in blood chloride, and dehydration is an established fact. Hastings, Murray and Murray found that in dogs, obstruction at the pylorus caused a reduction in the blood chloride to 50 per cent of the normal within a few days after the operation. Gamble and Ross confirmed this observation and made a more extended study of the changes in blood chemistry which follow pyloric obstruction. They consider that loss of chloride, by leading to a reduction in the electrolytes of the body, is the primary cause of the dehydration. They state that "a withdrawal of the electrolytes of the body fluids will be accompanied by a proportionate reduction in

the volume of body water and that this change can only be repaired by replacing both the lost water and the lost electrolytes," that is, the volume of body fluid is sustained by its content in total electrolytes. These observers showed that the loss of chloride in the vomitus is repaired for a time by the retention of carbon dioxide and the consequent increase in bicarbonate. By this means the concentration of electrolytes is maintained. In other words, the sum of (Cl^-) and (HCO_3^-) remains constant for a time (30 hours or so) after the obstruction has been established. A degree of alkalosis, however, results, which is countered by a loss of base (Na) in the urine; a reduction in (Cl^-) + (HCO_3^-) occurs. The

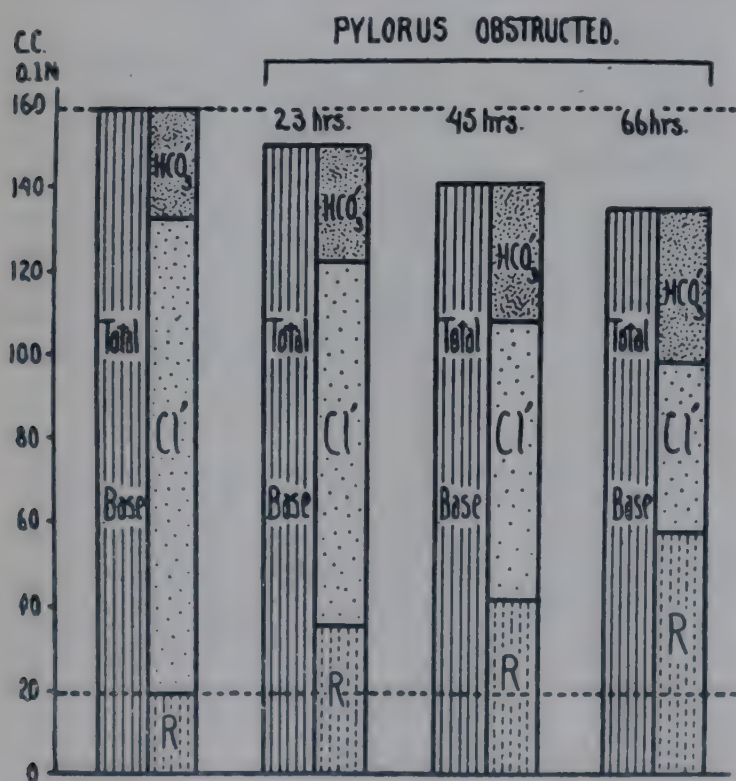


FIG. 213. Diagram to show change in the total content and distribution of electrolytes in the body fluids following pyloric obstruction. (After Gamble and Ross.)

reduction in ionic concentration of body fluids resulting from the depletion of base, which unlike Cl^- cannot be substituted for, is accompanied by a proportionate loss of water (fig. 213). These observers state that the value of sodium chloride injections in prolonging life in obstructed animals depends upon the fact that the replenishment of the stores of sodium permits the retention of water. Chlorides such as NH_4Cl or KCl are without any beneficial effect, nor will water alone or a solution of glucose prolong life.

The reduction in the blood chloride is not necessarily the result of vomiting. The accumulation of secretions above the point of obstruction will just as surely cause chloride depletion and dehydration. In the rabbit for example, which

cannot vomit, obstruction causes the characteristic blood changes. A most powerful stimulant to secretion is distension of the bowel wall; the dilated bowel in the later stages of obstruction thus becomes a receptacle for large quantities of fluid. In the case of the rabbit, fluid amounting to thirteen per cent or so of the body weight may be found in the stomach and bowel after death. The fatal effect of distension has been shown by Herrin and Meek. They distended a loop of bowel by means of a balloon and allowed the continuous secretion which resulted to drain to the exterior. The animals died in from 6 to 14 days. A loop of bowel opening to the exterior but not distended causes no injurious effect. Herrin and Meek concluded that the loss of chloride in the secretion was the essential factor leading to the death of their animals. Dragstedt and Ellis have also shown that the profound fall in blood chloride which follows the drainage of the gastric juice to the exterior is accompanied by grave symptoms and ultimately ends in death. The symptoms are rapidly relieved by the administration of saline. Fine and his associates have reported pronounced reduction in the plasma volume of patients suffering from acute obstruction of the small intestine.

There is no doubt that chloride loss and dehydration are important factors in the *later* stage of obstruction. The administration of saline is one of the most valuable measures possessed by the clinician for combating the condition at this stage either before or following operation.

Nevertheless, though the blood changes at this time undoubtedly prejudice the animal's chance of survival, it is unlikely that they play the primary rôle in causing death. For one thing, correction of the blood chemistry though it prolongs life is not curative. Moreover, death frequently occurs before any significant change in the blood chlorides takes place, while on the other hand, the blood chloride may be maintained at a level considerably lower than that usually seen in obstruction without the animal becoming moribund. The following experiments* indicate a nerve element as the primary cause of the train of symptoms seen in acute obstruction. A balloon was placed in the lower duodenum and distended to a pressure of about 100 mm. Hg. A large sized rubber tube attached to the balloon prevented any actual obstruction. X-ray examination showed that a barium mixture moved freely beyond the distended region. These animals

* Taylor, Weld and Harrison.

had symptoms indistinguishable from acute obstruction yet little fluid was lost by vomiting and the blood chlorides showed practically no change. On the other hand, otherwise normal animals who had had the blood chloride depleted by means of histamine injections (to stimulate gastric secretion) and apomorphine (to induce vomiting) remained in apparent good health even though the blood chloride had been maintained at a level 50 per cent below the normal for three weeks.

It is evident that in the balloon experiments just mentioned, distension of the bowel caused death in some way other than by chloride depletion. Another group of animals in which the bowel was distended by a balloon as described, but in which the segment of bowel had been first denervated survived for a much longer time than those in which a preliminary denervation had not been performed. This result indicates that afferent impulses arising from the distended segment of bowel are concerned in some way with the severe symptoms of obstruction. Herrin and Meek also observed that if a distended draining loop were denervated the animals survived indefinitely. They, however, offer an explanation of the benefit derived from denervation based upon the theory that dechlorination plays the essential rôle, namely, that when the vomiting and loss of appetite produced reflexly from the distended loop are abolished by nerve section, chloride loss is reduced and chloride ingestion increased. The importance of afferent impulses from the intestine in the production of the symptoms of obstruction therefore must be admitted; that they may cause death quite independently of dechlorination is evidenced from the experiments described in the last paragraph. It is well known that many reflex effects upon the cardio-vascular system and upon several important functions can be initiated from the gastro-intestinal tract. The

severe pain and collapse which result from the distension of other hollow viscera, e.g., the gall-bladder, stomach, kidney pelvis, etc., may also be recalled in this connection. Moreover, the severe symptoms and early death which result from the mere distension of the bowel by a balloon calls to mind the analogous clinical condition known as Richter's hernia. In this condition only a portion of the intestinal lumen is pinched off and isolated from the main passage. The bowel is not obstructed, yet all the symptoms of acute obstruction are present. It is quite conceivable that acute distension of the small isolated pocket by secretions and gas is responsible for the symptoms.

The contention of Zwemer and his associates that a high level of blood potassium is the cause of death in intestinal obstruction has not been substantiated by others. Keith and Binger, for example, raised the blood potassium of a group of normal persons and observed no harmful effects, and in patients suffering from obstruction there is a tendency for the potassium concentration of the blood to decrease rather than to increase (Falconer). In experiments with dogs Greenwood, Haist and Taylor found a significant rise in potassium as a terminal event only, and concluded, therefore, that hyperpotassemia was a factor of little importance as a cause of death in intestinal obstruction.

The importance of distension as a factor in acute obstruction of the intestine is now generally recognized and it has become the practice in suitable cases to decompress the bowel by suction-drainage through a tube passed from the mouth to the duodenum (Wagenteen and Paine) or, as in the method of Miller and Abbott, to insert a long slender tube through the nose into the stomach and allow it to be carried to the level of the obstruction. The tube has a double lumen and is provided at its tip with a small balloon which can be inflated after it has entered the duodenum. The balloon serves as a stimulus to peristalsis which carries it and the tubing along the bowel to the point of obstruction.

CHAPTER XLV

VISCERAL SENSATIONS

The abdominal and thoracic viscera are insensitive to the several types of stimuli which readily arouse sensations in the skin and more superficial tissues of the body. The effects of the different varieties of stimulus—*thermal, chemical, tactile* and *pain*—have been investigated by a number of observers including Ross, Head, Mackenzie, Hurst and Carlson.

Sensations of pain cannot be elicited from the viscera by the usual means. The intestine or the liver, the stomach or the heart may be cut, burned or pinched without arousing any immediate sensation. In the second stage of a colostomy operation, for example, the colon can be opened without pain being experienced by the patient. Harvey remarked upon the absence of sensation in the exposed heart of Viscount Montgomery.¹

The insensibility of the alimentary tract to ordinary forms of stimulation commences in the lower or middle third of the esophagus and extends as far as the commencement of the anal canal. How can these observations be reconciled with the well-known fact that pain is one of the commonest manifestations of visceral disease?

The whole subject of pain arising in or referred from the viscera is still of a highly controversial nature. No final answer can be given. The most that can be attempted is a summary of some of the more significant experimental results and clinical observations, and the opinions of those who have especially interested themselves in the subject.

Lenander considered that abdominal pain was always due to the stimulation of somatic nerve terminals in the parietal peritoneum or mesentery; the bowel itself was supposed to be quite devoid of pain fibers. According to this view therefore, pain localized within the organ itself—*true visceral pain*—was an impossibility.

Ross's theory postulated that visceral pain was

of two types: (a) *referred pain*, and (b) *visceral* or *splanchnic pain*, which was distributed poorly localized and arose in the viscus itself.

Mackenzie, as a result of his clinical observations strongly supported Ross's idea of referred pain, but maintained that *all* visceral pain of this nature, the viscera being quite insensitive to all forms of stimulation. In agreement with Lenander, he did not believe that the viscera contained pain fibers, true visceral pain was therefore never experienced.

Mackenzie's conception of referred pain

When a viscus is diseased, pain or tenderness is frequently felt in the tissues overlying it approximately (abdominal or chest wall) or in some quite remote from it. For example, pain is felt in the neck or shoulder (fig. 214) in conditions affecting the diaphragm, between the scapulae in gastric disease, or in the region of the umbilicus in appendicitis over the precordium or in the arm in angina pectoris (p. 280). When traction is made upon a coronary artery of a dog, the animal whines and indicates the location of the pain by limping on the left fore-paw. Other examples are, the pain in the perineum and tip of the penis caused by a stone in the region of the neck of the bladder, and the pain in the groin due to a stone in the ureter.

It will be recalled (p. 848) that a given segment supplies a visceral area with autonomic nerve fibers and a well-delineated area of the body (dermatome) with somatic nerves. The two areas of structure linked in this way through the spinal cord may be some distance apart (e.g., diaphragm and shoulder) or be more closely related (e.g., abdominal wall and an underlying abdominal viscus). Mackenzie believed that afferent autonomic impulses arising in a diseased organ, though of themselves incapable of arousing any sensation, would upon entering the cord set up an "irritation focus" with the result that cells accustomed to receive impulses from the corresponding somatic area were excited. Thus, the impulses from the viscera "irradiated" on to cells of the corresponding somatic center. New impulses originating in these cells travelled along the usual pathways to higher perceptive centers (thalamus) which

¹ Harvey records, "I carried the young man to the King (Charles I) that His Majesty might with his own eyes behold this wonderful case, that, in a man alive and well, he might, without detriment to the individual, observe the movement of the heart, and with his proper hand even touch the ventricles as they contracted. And His Most Excellent Majesty, as well as myself, acknowledged that the heart was without the sense of touch, for the youth never knew when we touched his heart."

ected or referred the sensation to the somatic area e.g., skin or muscle, from which it was accustomed to receive impulses. In this way, spontaneous pain in superficial structures remote from the diseased site was accounted for. Mackenzie spoke of these reactions as *viscero-sensory reflexes*." Tenderness to touch, pressure or light pinching of the skin (hyperesthesia and hyper-

indicating the referred nature of the pain. He explained the rigidity (hypertonus) of muscles overlying a diseased organ, the right rectus abdominis in acute appendicitis, for example, upon a similar basis. Afferent impulses of normal intensity arising in the muscle proprioceptors upon arriving at the spinal centers, which had been rendered hyperexcitable by the receipt of abnormal visceral impulses, resulted in a reflex increase in tonus of the corresponding muscles.

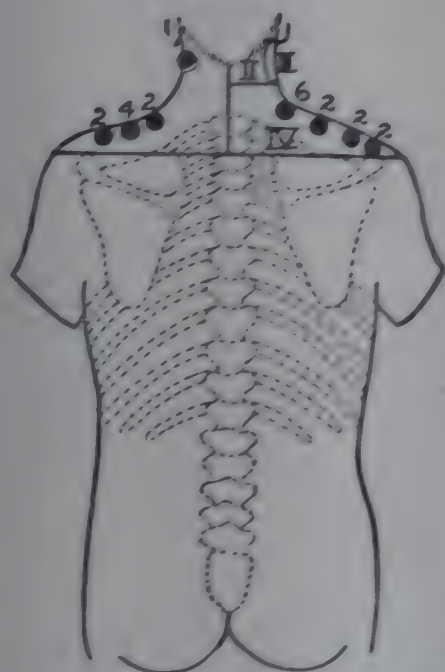
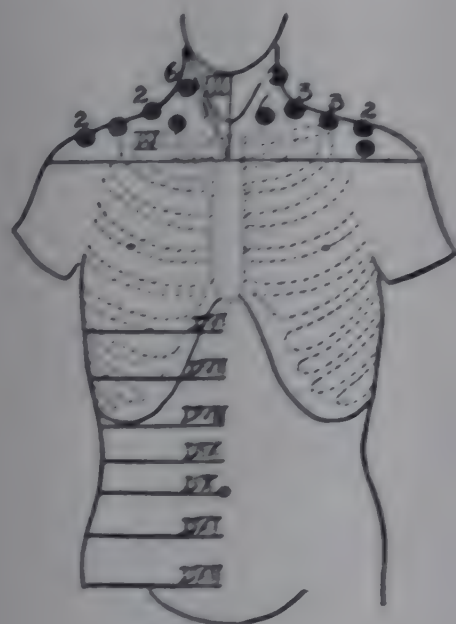


FIG. 214. Location of maximum points of referred pain from diaphragm irritation in twenty-three cases. They are all situated in the region supplied by the third and fourth spinal segments. (After Capps.)

esthesia) was ascribed to the impulses, which primarily would be below the threshold for pain, arriving in the segment rendered hyperexcitable as a result of impulses received from the diseased organ. In the case of the abdominal viscera, Mackenzie claimed that the area of tenderness in the abdominal wall remained fixed, though the position of the diseased organ changed, thus

TABLE 37*

VISCUS	SPINAL SEGMENTS
Lungs.....	1-7 dorsal, mostly 2-5 dorsal
Heart.....	3-5 cervical, 1-8 dorsal, predominantly on left side, sometimes bilateral
Esophagus.....	Mainly 5 dorsal, also 6, 7 and 8 dorsal
Breast.....	4 and 5 dorsal
Stomach.....	7, 8 and 9 dorsal, usually bilateral
Intestine.....	9-12 dorsal, bilateral or on left side only
Liver.....	8-10 dorsal on right side
Gall bladder....	Mostly 8 and 9 dorsal, also 5-7
Kidney.....	Mostly 10 dorsal, also 11 and 12 dorsal and 1 lumbar
Ureter.....	11 and 12 dorsal and 1 lumbar
Testis.....	10 dorsal
Epididymis....	11 and 12 dorsal
Bladder.....	11 and 12 dorsal and 1 lumbar, also 3 and 4 sacral
Prostate.....	10 and 11 dorsal, also 1-3 and 5 sacral
Ovary.....	10 dorsal
Fallopian tubes..	11 and 12 dorsal
Uterine cervix..	11 and 12 dorsal and 1-4 sacral
Uterine body....	10 dorsal to 1 lumbar

* From W. R. Brain, Diseases of the Nervous System, after Head.

The referred motor reaction he spoke of as a *viscero-motor reflex* (see fig. 215).

The conception of referred pain was supported by the work of Head, who mapped out the segmental distribution of the cutaneous nerves responsible for hyperesthesia in diseased states. This theory has gained wide acceptance.

In table 37 are given the segmental areas to which pain is referred in disease of various viscera (Head).

True visceral pain

True visceral pain, though denied by Mackenzie, exists. The pains of childbirth, for example, or

the pain of intestinal colic or of an over-distended bladder are undoubtedly felt in the organs themselves. Also in transection of the cord resulting in complete paralysis and anesthesia of the abdominal wall intestinal pain is experienced, which obviously cannot be due to reference to somatic nerves. Impulses in such cases must have reached the central nervous system along intact visceral (autonomic) afferents and either have entered the cord by the posterior roots above the point of transection or have been conveyed by the vagus. It has not been definitely demonstrated that the sensation of pain can be conveyed by the

many disease of the appendix. A distinction should be drawn between pain of this nature and referred pain.

The adequate stimulus for visceral pain

The existence of true visceral pain is not incompatible with the statement made above that the viscera are insensitive to the ordinary type of stimulus. Hurst's experiments indicate that the only adequate stimulus for visceral pain fibers is tension. Distension of a hollow viscus e.g., stomach, intestine, gall-bladder, etc., give rise to pain as a result of the stretch stimulus applied to the nerve terminals in its wall. The pain may be either roughly localized to the viscus itself, or referred.

Though the question is by no means settled, it appears that contraction of the muscular wall of a hollow viscus does not of itself give rise to pain. Pain arises, however, if the contraction causes distension of a neighboring portion of the wall as may result when the contraction wave approaches a mechanical obstruction, a length of bowel in spasm or a sphincter which fails to relax (*achalasia*). Poulton, for example, found that when a balloon was inserted into the lower part of the human esophagus, the approach of a peristaltic wave toward the obstruction caused pain, but during its passage over the esophageal wall in contact with the balloon no sensation was felt. Poulton attributes the absence of pain during the passage of the contraction wave to the reduction in the diameter of the tube and the consequent relief from stretch of the nerve endings lying between the muscle fibers. Pain also ceased if the esophageal muscle relaxed to accommodate the balloon; that is, adjusted the length of its fibers to the distending force (postural tone, see p. 47). As further evidence for the effectiveness of distension in causing pain, the following observations may be cited. In animals, when an intestinal loop exposed under local anesthesia is stimulated to powerful contraction, there is no evidence of pain, whereas even moderate distension of the loop (as by inflating it with a balloon) is manifestly painful. Distension of the gall-bladder of the cat is accompanied by reactions indicative of intense pain. Distension of the human appendix by the injection of fluid through an appendicostomy opening causes severe pain in the epigastrium or in the region of the umbilicus and when the duodenum is distended by the injection of material through a duodenal tube, pain is felt on the right side. The pain impulses

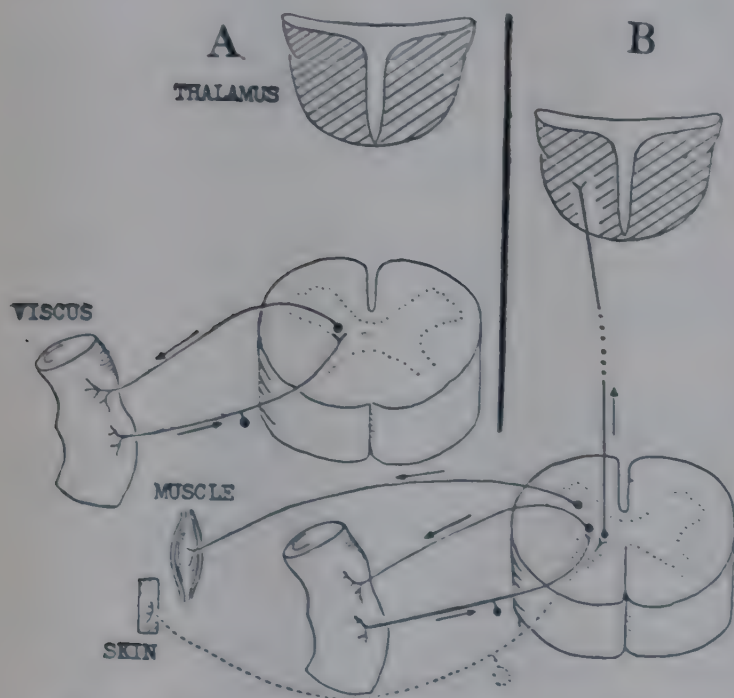


FIG. 215. Diagram to illustrate Mackenzie's theory of referred pain. A, representing normal conditions, a visceral reflex is shown. B, illustrates a visceromotor and a viscerosensory reflex. Impulses from a viscus are conceived as setting up an irritable focus in the cord which through the involvement of neighboring neurons increases the tone of muscles innervated by the same segment, and causes a discharge of impulses over the pathway for pain. The sensation is then projected in consciousness to the periphery, as indicated by the dotted line.

afferent fibers of the vagus, but it is possible if not probable that such is the case. Pain arising in the viscera is diffuse, poorly localized and often of a dull, boring character. These features are characteristic of protopathic sensibility in general, and the viscera apparently are supplied only with fibers capable of conveying this type of sensation. The impulses responsible for this primitive type of sensation are believed to ascend no higher than the thalamus (p. 880).

Pain in a normal viscus may result from disease in a distant organ through a visceromotor reflex. Painful pylorospasm, for example, may accom-

doubtedly reach the central nervous system through the splanchnic nerves. Bentley and Smithwich distended the duodenum of patients whose splanchnics had been divided on one or on both sides. After unilateral denervation, distension caused pain on the denervated side only; no pain whatever was felt after bilateral splanchnic section.

Morley's theory of abdominal pain

Morley contends that the referred pain of abdominal disease does *not involve autonomic afferents* as postulated by Mackenzie but is due to the stimulation of *somatic* pain fibers in the parietal peritoneum or mesentery, the sensation being referred to the superficial area innervated from the same segment. He expresses what he terms the *law of referred pain* in the following words. *Referred pain only arises from irritation of nerves which are sensitive to those stimuli that produce pain when applied to the surface of the body.* He believes that the somatic innervation of the peritoneum extends along the mesentery to within a short distance of its attachment to the bowel and does not terminate as has been generally supposed near the root of the mesentery.² The mesentery or peritoneum is therefore sensitive to tearing, cutting, etc., whereas the organ itself which contains only autonomic afferents is insensitive to these types of stimulus. In support of his views Morley cites the pain in the shoulder associated with irritation of the peritoneal covering of the diaphragm. He points out that the diaphragm is innervated (through the phrenic) chiefly by the fourth cervical spinal segment and to a less extent by the third and fifth. None of these segments give rise to autonomic fibers but the third and fourth cervical nerves furnish somatic afferent fibers to the shoulder area in which the referred pain of diaphragmatic disease is located. Morley explains muscular rigidity in a similar manner—the radiation of impulses over motor nerves. He replaces Mackenzie's terms, viscerosensory and visceromotor reflexes by *peritoneo-cutaneous ra-*

diation and peritoneo-muscular radiation respectively. Morley also recognizes true visceral pain resulting from an adequate stimulus—, namely, tension. The pain and tenderness resulting from pressure upon an inflamed viscus (e.g., ulcer of the duodenum) through the abdominal wall he ascribes however, to the parietal peritoneum being brought into contact with the roughened surface of the lesion. As evidence that the sensation is not, in such instances, referred to the skin from the diseased structure, but is due to the stimulation of nerves in the parietal peritoneum he states that (a) the area of tenderness shifts with the movement of the viscus, (b) the tenderness is not abolished by infiltration of the skin with novocaine, and (c) direct pressure upon the inflamed organ when exposed by operation in a conscious patient (i.e., under local anesthesia) does not give rise to any sensation. Morley has made out a case for the production of pain in some instances through a peritoneo-cutaneous reaction, and for pain and tenderness upon pressure being the result of the stimulation of somatic nerves in the parietal peritoneum. Nevertheless, it is probable that referred pain in other instances is brought about through the mediation of both visceral and somatic nerves (viscero-sensory reflexes). Woollard and Carmichael, for example, have obtained evidence for the latter from experiments upon the human testis which, since it has migrated from the abdominal cavity and is enveloped by peritoneum, may be looked upon as an abdominal organ, in so far as the question of referred pain is concerned. These observers found that after all the nerves to the testis had been blocked by means of novocaine, except the autonomic fibers passing along the spermatic artery, no sensation was felt within the organ when it was compressed; but pain, referred to the tenth dorsal segment—lower abdomen and back—was experienced. Moreover, pain is unquestionably referred from the heart (e.g., in angina pectoris) to the left arm and from the biliary tract to the inter or subscapular region.

An explanation of referred pain on the basis of reflex vasomotor changes or the liberation of a chemical substance at somatic nerve endings

Pollock and Davis stimulated the peritoneal surface of the diaphragm in dogs. The animals showed every sign of suffering pain, which was abolished by any one of the following procedures. Section of the phrenic nerve; removal of the cervical sympathetic chains; severing the eighth cer-

² Sheehan has made a study of the nerves of the mesentery and finds the following types of fiber:

(1) Fibers ending in Pacinian corpuscles scattered throughout the mesentery. These are afferent sympathetic fibers which travel in the splanchnic nerves.

(2) Free non-myelinated fibers. These are afferent and efferent sympathetic fibers; their terminals are distributed to the serous covering of the bowel. They provide a medium for the transmission of true visceral pain.

(3) Free myelinated fibers derived presumably from somatic nerves. These apparently do not extend as far as the serous covering of the bowel itself.

vical and the first, second and third thoracic anterior roots; transection of the cord at the seventh cervical segment; destroying the cord at the first and second dorsal segments; or section of the cervical posterior roots. Pollock and Davis conclude from these results that the pain impulses following stimulation of the diaphragm travel over the phrenic, enter the cord by the posterior cervical roots, descend the cord to the level of the eighth cervical and first, second and third thoracic segments. Connections are then made with cells in the lateral horn of gray matter (intermediolateral column) from where impulses pass by sympathetic preganglionic fibers to the cervical sympathetic chain, and then by postganglionic fibers "to the skin, blood vessels, meninges and other structures, where by some vasomotor (?) or hormonal (?) process the sensory endings of the cerebro-spinal system are stimulated and a sensory impulse travels over the ordinary cerebro-spinal system, enters the spinal cord by the posterior roots and ascends to consciousness."

The experiments of Lewis and Kellgren

Lewis and Kellgren agree with Lenander, Mackenzie and Morley that the bowel itself is not innervated by fibers mediating the sensation of pain. They argue that did such fibers exist they should give rise to pain when stimulated in other ways than by tension, such as by cutting, pinching or burning. In support of this view, they point out that though light waves constitute the adequate stimulus for the visual receptors, the fibers of the optic nerve respond to mechanical stimulation, such as cutting, by a flash of light (see p. 959). It is claimed that the pain caused by contraction or distension of the bowel is due to traction upon the mesentery and the stimulation of the pain fibers contained therein.

These investigators have carried out experiments upon a number of human subjects; their results are highly significant to the question of referred pain. Pain closely resembling in character the referred pain of visceral disease was induced by the injection of a small quantity (0.3 cc.) of hypertonic saline into an interspinous ligament at various spinous levels. Injection into the 1st lumbar interspinous ligament caused pain distributed in a manner strikingly similar to the pain of renal colic, namely, in the loin and in the inguinal and scotal regions. The pain was accompanied by retraction of the testis. Injection into the 9th thoracic interspinous ligament caused pain in the back in the region of the 1st lumbar spine and over an area in front extending from the 9th costal cartilage on the affected side to the umbilicus. Rigidity of the ab-

dominal muscles and deep tenderness were associated with the pain. Stimulation of the 8th cervical ligament was followed by pain in the interscapular region, over the pectoralis major muscle and down the inner side of the elbow and forearm, together with a sensation of constriction in the upper part of the chest on the stimulated side. Several subjects of angina pectoris were chosen for experiment and were asked to compare the pain which they experienced in an attack with that caused by the stimulation of the 7th cervical or the 1st thoracic interspinous ligament. In all instances the patients described the experimentally induced pain as being identical in character with that caused by the disease, though it showed some minor differences in distribution.

Lewis and Kellgren also found that in cats mechanical stimulation (pinching) of the pancreas or of the mesentery in the duodenal loop, caused motor reflexes from the abdominal muscles which resembled closely those caused by stimulation of the back muscles. The muscular responses were abolished by section of the splanchnic nerves.

Lewis and Kellgren have drawn the conclusion from their results that the pain of visceral disease and the pain arising in deep somatic structures, i.e., all deep-seated pain, is mediated by a common system of nerves. In their opinion there is no physiological justification for placing visceral pain in a special category. Though one pain is mediated by fibers which have their endings in the mesentery and omentum and travel with sympathetic efferents (see page 942), and the other by fibers which terminate in somatic structures, both enter the central nervous system by the posterior nerve roots, and there is no indication that their courses within the cord or their central terminations are not identical. So-called referred pain, they suggest, is simply a matter of localization, which is precise in superficial structures, innervated by one part of a spinal segment, but more diffuse and inaccurately localized in deep structures innervated by another part of the same segment. It is this diffuse type of pain which has been called "referred." Thus, they maintain, there is no necessity to postulate an irritable focus in the cord through which a somatic and a visceral system of nerves are linked.

THE SENSIBILITY OF THE ALIMENTARY TRACT TO TACTILE, THERMAL AND CHEMICAL STIMULATION

Touch. The sensation of touch disappears at the lower end of the pharynx. This was shown by Hurst by means of an esophageal tube with a slit on one side through which the mucosa of the esophagus could be stimulated. Carlson, by means of a test-tube brush passed into the stomach, was unable to elicit the sensa-

tion of touch from the gastric mucosa. The rectum possesses no tactile sensibility but the anal canal is sensitive.

Thermal sensibility. The esophagus is sensitive to extremes of heat and cold. The sensations of temperature that are felt when hot or cold materials enter the stomach have been thought by some to originate in the lower end of the esophagus, by others to arise in the skin of the epigastrium, either through thermal conduction or by reflex changes in the cutaneous blood vessels. Carlson has shown, however, that the gastric mucosa is sensitive to extreme temperature changes, i.e., protopathic thermal sensibility (below 13°C. or above 45°C.). It is the lower end of the esophagus, however, which is responsible for the greater part of the thermal sensation that is experienced when excessively hot or cold materials are swallowed. This is due to the greater sensitivity of the esophageal mucosa, as well as to the fact that the material is retained for an appreciable length of time above the cardia. The colon is insensitive to temperature changes, but even comparatively slight differences in temperature can be detected in the anal canal.

Chemicals, with the exception of alcohol, cause no sensation whatever when introduced into the stomach or intestinal canal. The mucosa is completely insensitive to acids; the introduction into the healthy stomach of a solution of 0.5 per cent hydrochloric acid causes no pain or sensation of any kind. Alcohol stimulates the mucosa of the esophagus and stomach and causes a sensation of warmth. Peppermint and various condiments free from alcohol arouse no sensation. The pelvic colon and rectum show a similar sensitivity to alcohol but are insensitive to other chemicals. The anal canal is extremely sensitive especially to alcohol and glycerine. Both cause a burning sensation.

NAUSEA

Nausea usually precedes the act of vomiting (p. 490) but may occur alone. On the other hand vomiting may occur without nausea, as in certain cerebral conditions. The sensation is felt in the back of the throat or pit of the stomach, and in its milder degrees is merely a "sinking" sensation in the epigastrium. It is frequently associated with vasomotor disturbances and sweating. Increased tension upon the walls of the stomach or duodenum is a potent cause of the sensation, and Poulton has shown that it is also induced by distension of the lower part of the esophagus. During the passage of a peristaltic wave which relieves the tension upon the nerve fibers (p. 516) in the esophageal walls the sensation is relieved. Barclay showed by radioscopy in the human subject that nauseous odors caused the lower border of the stomach to descend an inch or two evidently as a result of sudden relaxation of the abdominal

muscles. This movement would tend to stretch the esophagus and gastric walls and so exert tension upon the nerve endings. The stimulus which induces nausea is, therefore, the same, apparently, as that which causes visceral pain, but of lower intensity. It is likely that the sensations experienced during changes in speed of an elevator is also the result of tension exerted upon the esophagus and gastric walls. This element is also probably a contributory factor in the production of sea sickness, being brought into play by the pitch and roll of the ship (p. 493).

The relief of nausea and vomiting by the application of counter irritants to the epigastrium or over the sternum is probably due to either a reflex change in the postural tone of the gastric walls or to the reflex initiation of peristaltic contractions (p. 516). The tension upon the nerve endings in the latter instance is taken up by the muscle fibers. Poulton observed, for example, that the sensations caused by a balloon in the esophagus were relieved by vigorous friction of the skin over the sternum; contraction of the esophagus in some cases or adjustment of the postural tone of the esophageal wall in others were observed to accompany the disappearance of the sensation.

HUNGER AND APPETITE

Since these sensations are so frequently associated they tend to be confused in consciousness and it is often difficult to separate them clearly. The two are, however, essentially different, and appetite is not merely a less intense degree of hunger. The sensation of appetite may be experienced when the stomach contains plenty of food, and is therefore quite independent of hunger. On the other hand, though hunger is usually accompanied by keen appetite, this is not necessarily so. It is well known that the appetite may be lost though a feeling of emptiness and hunger be present. The two sensations also differ in that one (hunger) is unpleasant, while the other is pleasant (Ryle).

Hunger is a gastric sensation and is due to the strong peristaltic contractions that arise in the stomach when it is empty or nearly so (p. 493). These may cause a sense of discomfort or actual pain—the pangs of hunger. The normal sensation of hunger is believed to be a purely local one, arising in the gastric region, and is not directly dependent upon the state of the blood or any state of the general tissues of the body. The local nature of the hunger sensation is evidenced by several observations. Cannon and Washburn showed clearly the relation of the contractions of

the empty stomach to the sensation of hunger. The following facts indicate that hunger is not due to a general bodily state. It is aroused while the intestine still contains plenty of unabsorbed food, and becomes less intense in prolonged periods of starvation. Filling the stomach with bulky material that possesses little nutritive value, or is indeed totally inedible, inhibits the contractions characteristic of the empty organ, relieves the pangs of hunger and may even create a feeling of satisfaction. This fact has some practical bearing in the treatment of obesity, since the subject may satisfy himself with foods such as salads, fruits, etc., possessing large volume relative to their caloric values.

Though the importance of the gastric element in the production of hunger cannot be denied, the occurrence of this sensation has been reported after complete gastrectomy. Afferent impulses from the duodenum were probably responsible in these instances; they likely play a part also under normal circumstances. The sensation of emptiness which is frequently associated with "rumblings" (borborygmi) in the small bowel, is also probably of intestinal rather than of gastric origin.

Appetite, on account of its complex nature and vague localization, is a more difficult sensation to define; some persons refer it to the pharynx or esophagus, others to the stomach. It is probably to a large degree acquired rather than inborn like the hunger sensation. That is to say, it is dependent upon previous experience; and conditioned stimuli (p. 907) enter largely into its causation. A new-born infant experiences hunger but probably not appetite. Nevertheless, it appears that there is also a purely gastric element in the production of appetite. For example, alcohol, by stimulating the gastric mucosa, causes a sensation of warmth within the stomach, raises gastric tone and arouses appetite. According to Carlson hydrochloric acid does likewise, and the flow of gastric juice induced by the taste of food may well serve the purpose of augmenting the appetite in the initial stage of digestion. It is well known that appetite is often greatly increased after the first few mouthfuls have entered the stomach, and though the effect produced by the taste of the food is difficult to exclude, the fact points to a gastric element. Pavlov has reported, as his own experience, the pronounced effect which a glass of wine, after reaching the stomach, had in restoring the lost appetite following an illness. There is also some evidence that impulses arising not only from the mucosa but from the deeper

structures of the gastric walls play a part and that increased muscular tone is a factor in the production of appetite. The smell of a disgusting material may, as we have seen (p. 519) cause a sudden lowering in the position of the stomach, an increased tension to be exerted upon its walls, and a sensation of nausea—the antithesis of appetite. Conversely an increase in the tone of the gastric muscle, by reducing the stretch upon the nerve terminations of the stomach wall, would conceivably be conducive to gastric comfort and well-being, leading to the appetite sensation. In fasting the gastric tone is also high and this may well be the cause of the keen appetite usually associated with hunger; the latter, on the other hand, as stated above, may be ascribed more particularly to the rhythmic contractions. Support for the conception that gastric tone is an important factor in the production of appetite is offered by X-ray examination of the stomach in various conditions associated with disorders of appetite. In those diseases in which a poor appetite is a prominent feature the gastric tone is low, and in others characterized by excessive appetite, the stomach is very frequently hypertonic. The association of loss of appetite and gastro-intestinal hypotonicity in B_{12} deficiency (p. 642) may also be recalled in this connection. Barclay has recorded experiments upon hospital patients in whom the sight or smell of appetizing food was responded to by an increase in gastric tone. In some the mere suggestion of a glass of beer was sufficient to bring this about. On the other hand, mental states, e.g., anxiety, worry, fear, etc., which lower gastric tone, also depress the appetite. The probability of appetite having its origin, in part at least, in the walls of the stomach is indicated by what Ryle considers a very significant fact, namely, that in diffuse carcinoma of the stomach ("leather bottle" stomach) loss of appetite is a prominent and almost constant symptom. In other diffuse types of gastric carcinoma, even though far advanced, the appetite may be retained. Bitters and other so-called appetizers unless made with alcohol exert no effect upon the appetite. Insulin, owing to its hypoglycemic action, stimulates appetite (p. 585); it also increases gastric tone.

Anorexia nervosa. A mental state leading to complete loss of appetite, or what really amounts to a morbid distaste for food of all sorts, was first described by Sir William Gull some 65 years ago and named *anorexia nervosa*. The subjects are usually nervous "high-strung" women. Some emotional upset may precipi-

tate the condition. Extreme emaciation, low metabolic rate, moderate hypoglycemia and amenorrhea are among the chief features. The appearance of the patient may suggest pituitary cachexia (Simmonds' disease, p. 738). Profound exhaustion results and death may occur from starvation. The aversion to food appears to be purely psychic, there being no evidence that some endocrine function is primarily at fault; nor is there any indication of organic gastric disease.

Thirst. The sensation of thirst is referred to the pharynx and is due to the stimulation of sensory nerve endings in this situation. Two theories have been advanced to explain the mechanism by which the sensation is aroused.

According to one view, thirst is due simply to the drying of the pharyngeal mucous membrane, the salivary glands being given a rôle in the regulation of the water balance of the body. When the water content of the body falls below a certain level salivary secretion is depressed, the consequent drying of the mucous membrane of the throat then elicits the characteristic sensation. If such a view is correct, drying of the pharyngeal mucosa from whatever cause should cause thirst. Cannon, who is the chief supporter of this theory, found in studies upon himself that after abstinence from fluids for a time the depression of salivary secretion which resulted was definitely associated with thirst. Atropine, which inhibits salivary secretion, also produced the typical sensation, and thirst aroused by the deprivation of water was relieved by the application of cocaine to the mucosa. Pilocarpine is also said to relieve thirst. In dogs, however, atropine and pilocarpine are without effect upon the water intake.

According to the other view, the thirst sensation is due to changes in blood composition, probably to a rise in its osmotic pressure, which stimulates the afferent nerve endings; or acts perhaps upon central nervous structures. Rowntree and his associates, for example, found that the thirst of diabetes insipidus was relieved neither by cocaineization of the mucous membrane nor when salivation was induced by pilocarpine. The experiments of Gilman suggest that cellular de-

hydration rather than a rise in osmotic pressure is the prime factor in arousing thirst. Elevation of the osmotic pressure of the blood in dogs, induced by the intravenous injection of hypertonic solutions of NaCl, caused a much greater intake of water than an equivalent rise in osmotic pressure caused by the injection of urea. After NaCl administration the ingested water quickly reduced the osmotic pressure of the blood to the pre-injection level, whereas after the injection of urea the osmotic pressure remained elevated. In support of the view that a lowered water content of the cells is the true thirst stimulus, Gilman cites an experiment in which anhydremia was induced by the withdrawal of large quantities of extracellular electrolytes (e.g., NaCl) without the withdrawal of water. In such anhydremic animals hydration of the tissue cells occurs, and though the oral mucous membranes are quite dry there is no evidence of thirst—water is refused.

It is not possible to make a definite choice between the two theories; evidence can be cited in support of either. It is probable that the factors concerned in the production of the sensation are both local and general. Experiments upon dogs in which the salivary glands were extirpated might be expected to provide a decisive answer. Such procedures however, have yielded conflicting results. Though some observers have reported an increased water consumption after the operation, others have been unable to obtain any evidence that removal of the glands induced thirst.³ A positive result, nevertheless, carries more weight than a negative one since mucus-secreting glands are scattered diffusely over the mucosae of the buccal and pharyngeal cavities.

The sensations and severe nervous symptoms which result from prolonged water deprivation are, of course, general in character and cannot be attributed to simple drying of the pharyngeal mucosa. They are dependent, no doubt, upon changes in blood composition and the dehydrated state of the tissues (p. 17).

³ See Montgomery, M. F., and Gregersen, M. L. and Cannon, W. B.

SECTION VI. METABOLISM AND NUTRITION

CHAPTER XLVI

GENERAL METABOLISM

Metabolism is the term employed to embrace the various chemical processes occurring within the tissues upon which the growth and heat production of the body depend and from which the energy for muscular activity and for the maintenance of vital functions is derived. *Catabolism* is the term employed to embrace chemical reactions involving the breakdown or decomposition of substances into their simpler constituents. *Anabolism* is the word used to connote building up or assimilative processes.

HISTORICAL SURVEY AND GENERAL PRINCIPLES

The modern science of metabolism may be taken to date from the experiments of Lavoisier, carried out toward the end of the eighteenth century. He demonstrated that animal heat was the result of the oxidation of carbon in the body, and compared the process to the burning of a candle or any other combustible material. The process in either case involved the consumption of oxygen and the formation of carbon dioxide. Lavoisier and the physicist Laplace placed a guinea-pig in a closed chamber and determined the quantity of carbon dioxide eliminated in a 10-hour period. The same quantity of carbon dioxide was found to be produced by the animal's body as when 3.3 grams of pure carbon were burned in air. The guinea-pig was next placed in a closed space surrounded by ice. The heat given out by the animal's body during a 10-hour period was calculated from the quantity of ice which had melted (fig. 216). Three and three-tenths grams of carbon burned in a similar ice calorimeter were found to generate an amount of heat comparable with that given off by the animal. It was therefore concluded that the heat generated by the animal and the carbon dioxide eliminated by the lungs were the result of the combustion of approximately 3.3 grams of the body's carbon. *Thus, the parallelism between the amount of heat generated in the animal body and the quantity of carbon dioxide eliminated was demonstrated.*¹ A few years earlier Crawford, using a water calorimeter, had demonstrated a parallelism between the oxygen used and the heat generated. He found that a guinea-pig gave out a definite quantity of heat for every 100 ounces of oxygen

¹ Lavoisier, however, believed that the heat was produced through the oxidation of carbon and hydrogen in the lungs. Not until some years later was it shown that the site of the heat production was the result of the combustion of foodstuffs in the various tissues of the body.

which it consumed. When this quantity of oxygen was used in the burning of carbon outside the body, approximately the same quantity of heat was produced.

A summary of the work of later investigators and of the fundamental principles upon which modern studies in metabolism are based will now be given.

(1) Heat values of the foodstuffs

About half a century after the experiments of Lavoisier the work of Joule (1842) demonstrated the mechanical equivalent of heat, and Mayer and Helmholtz (1845) discovered the law of the conservation of energy which states that the sum total of energy in the universe remains constant, but that one form of energy, potential, mechanical, electrical, etc., may be converted into another. Through the work of Voit, Pettenkofer and Rubner this law was shown to hold true for the animal body. Rubner determined the heat produced by the three types of food when burned outside the body in a calorimeter and thus established their heat values. He then measured directly the heat given off by a dog placed in a calorimeter and found that for fat and carbohydrate the heat production was the same within experimental error whether combustion occurred within or outside the body. For protein the heat production was less when metabolized (*physiological heat value*) than when burned in a calorimeter. The reason for this is that unlike carbohydrate and fat, which are completely oxidized in the body to CO_2 and water, the combustion of protein by the tissues is incomplete. The carbon part of the molecule is burned but the nitrogen is excreted in the urine as urea and other nitrogenous compounds which possess a certain energy value. Burned outside the body, protein yields 5.3 Calories as compared with its physiological heat value of 4.1. The following are the quantities of heat generated by the metabolism of 1 gram of the respective foodstuffs:

1 gram of fat	yields 9.3 Calories
1 gram of carbohydrate	yields 4.1 Calories
1 gram of protein	yields 4.1 Calories

The caloric values of different types of carbohydrate and protein are not identical. The value for starch, for example, is 4.20 and for sugar 3.96. The value is higher for animal than for vegetable protein. There is also a small energy loss during digestion. For these reasons the respective values for fat, carbohydrate and protein in a mixed human diet are usually taken at 9.0, 4.0 and 4.0 respectively.

most cases over several days, when added to the heat equivalent of the excreta (urine and feces) was found to correspond, within about 1 per cent, to the calculated heat value of the ingested food. In other words, the energy intake and output balanced and the application to the body of the law of the conservation of energy was demonstrated. (See table 38.)

Corresponding results were obtained by Atwater for man. Rubner also demonstrated that the heat production of an animal as measured directly (direct calorimetry) agree within 1 per cent of that calculated indirectly from the respiratory exchanges (indirect calorimetry)—a brilliant confirmation of the conclusion arrived at by Lavoisier 100 years earlier.

(3) The respiratory quotient

Since the relative amounts of oxygen and carbon contained in the molecules of the three food-stuffs differ, the relative volumes of oxygen consumed and of carbon dioxide produced during the metabolism of each type of food also varies. The ratio $\frac{\text{vol. CO}_2 \text{ expired}}{\text{vol. O}_2 \text{ inspired}}$ is called the respiratory quotient or, briefly, the R. Q.

The following equation represents the oxidation of glucose:



It is clear from this equation that no oxygen is required from a source outside the food itself for the oxidation of the hydrogen in the glucose molecule, and that for each molecule of O_2 absorbed a molecule of CO_2 is produced. It will also be recalled that according to the law of Avogadro quantities of any two gases containing the same number of molecules and under identical conditions of temperature and pressure have equal volumes. In the metabolism of 100 grams of glucose, 75 liters of oxygen are required from the outside for its complete combustion, i.e., for the oxidation of the carbon; 75 liters of carbon dioxide are therefore produced. The respiratory quo-

tient, then is, $\frac{75}{75} = 1.0$. For the combustion of 100 grams of fat, (e.g. triolein $C_3H_5(C_{18}H_{33}O_2)_3$), which is rich in carbon and hydrogen but relatively poor in oxygen, 200 liters of the latter gas are required; 142 liters of carbon dioxide and about 110 grams of water are produced. The R.Q. is therefore $\frac{142}{200} = 0.71$. The R.Q. of protein is

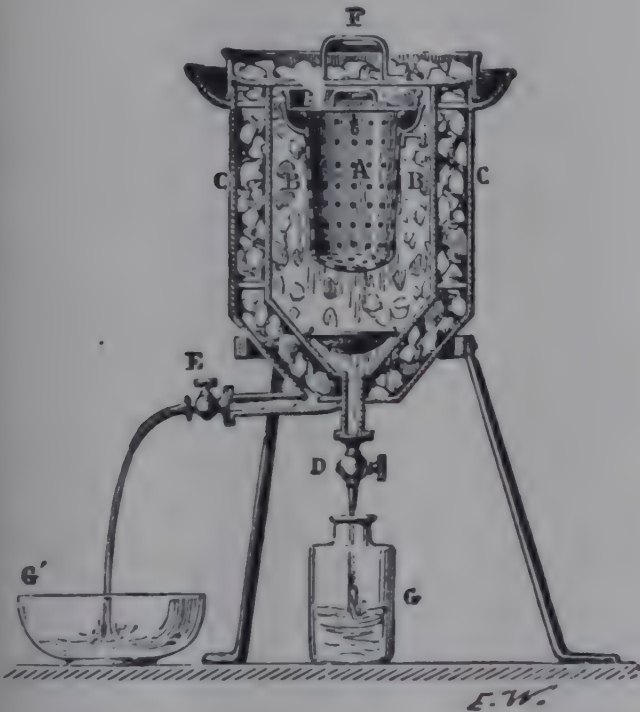


FIG. 216. Ice calorimeter of Lavoisier and Laplace. (After Luciani.)

TABLE 38*
Comparison of estimated heat from metabolism of food with heat actually produced

FOOD	NUM- BER OF DAYS	HEAT CALCU- LATED	HEAT DIRECTLY DETERMINED	DIFFERENCE IN PERCENTAGE
		cal.	cal.	
Starvation.....	5	1296.3	1305.2	-1.42
	2	1091.2	1056.6	
Fat.....	5	1510.1	1498.3	-0.97
Meat and fat. ...	8	2492.4	2488.0	
	12	3985.4	3058.4	
Meat.....	6	2249.8	2276.9	-0.42
	7	4780.8	4769.3	+0.43

* From Lusk after Rubner.

(2) The energy balance

Rubner placed a full-grown dog in a calorimeter (p. 526) in which the heat production could be measured directly. He fed the animal measured amounts of food for which the actual heat values had been calculated. The heat generated by the animal during the experiment, which extended in

0.80 and of alcohol 0.67. The value of the respiratory quotient is taken as an indication of the *type* of food being metabolized. It gives no quantitative estimation of the metabolism. An R.Q. around unity is taken to indicate that the material being used is chiefly carbohydrate; one around 0.70 indicates that it is mainly fat.²

On an ordinary mixed diet the respiratory quotient is about 0.85 and in the postabsorptive state (p. 533) about 0.82. In the formation of fat from carbohydrate, as in the fattening of farm animals, an oxygen-rich substance is being converted into one poor in oxygen. Oxygen is liberated in the conversion and less, in consequence, is taken in from the outside for general oxidative processes. The respiratory quotient may therefore rise above unity (up to 1.4). A very low quotient, as is seen in the hibernating animals, is supposed by some to indicate the reverse process, i.e., the conversion of fat to carbohydrate. In the hibernating marmot the R.Q. is between 0.6 and 0.7.

(4) Thermal Equivalents

As mentioned on page 522 the heat production bears a relation to the oxygen consumed and the carbon dioxide eliminated. Consequently, if one knows the quantity of either of these respiratory gases consumed or exhaled, respectively, during a given period, the heat production of the body during that time can be calculated. The heat production for a given quantity of these gases varies, however, with the type of food undergoing combustion. For instance, when carbohydrate is burned the consumption of a liter of oxygen causes a greater evolution of heat (5.047 Cal.) than when fat is burned (4.686 Cal.). This is so because a larger part of the oxygen required for the complete combustion of the former substance is, as mentioned above, contained within its own molecule. The value for protein is 4.485 Calories. The heat equivalent of CO₂ varies much more than does that of oxygen; for example, a liter of CO₂ formed in the combustion of carbohydrate represents the evolution of 5.047 Calories, whereas, the heat equivalent of this volume of CO₂, when the fuel is fat, is 6.629 Calories.

It is therefore more usual to calculate the heat production from the oxygen consumption; but

² Cathcart and Markowitz point out, however, that probably too much reliance has been placed upon the value of the respiratory quotient as an unequivocal criterion of the type of foodstuff undergoing metabolism. The R.Q. in a given instance is undoubtedly a resultant of several different metabolic processes—syntheses and interconversions as well as combustion.

even so, the food mixture undergoing combustion, as indicated by the respiratory quotient, must be taken into account. The heat or caloric values (thermal quotients) of a liter of oxygen at different respiratory quotients is given in table 39 compiled by Zuntz and Schumburg (as modified by Lusk).

In table 39 the percentage of fat and carbohydrate undergoing combustion have been calcu-

TABLE 39
(After Zuntz and Schumburg, modified by Lusk*)

NON-PROTEIN RESPIRATORY QUOTIENT	CALORIES PER LITER O ₂	CALORIES DERIVED FROM	
		Carbohydrate	Fat
		<i>per cent</i>	<i>per cent</i>
0.707	4.686	0	100
0.71	4.690	1.10	98.9
0.72	4.702	4.76	95.2
0.73	4.714	8.40	91.6
0.74	4.727	12.0	88.0
0.75	4.739	15.6	84.4
0.76	4.751	19.2	80.8
0.77	4.764	22.8	77.2
0.78	4.776	26.3	73.7
0.79	4.788	29.9	70.1
0.80	4.801	33.4	66.6
0.81	4.813	36.9	63.1
0.82	4.825	40.3	59.7
0.83	4.838	43.8	56.2
0.84	4.850	47.2	52.8
0.85	4.862	50.7	49.3
0.86	4.875	54.1	45.9
0.87	4.887	57.5	42.5
0.88	4.899	60.8	39.2
0.89	4.911	64.2	35.8
0.90	4.924	67.5	32.5
0.91	4.936	70.8	29.2
0.92	4.948	74.1	25.9
0.93	4.961	77.4	22.6
0.94	4.973	80.7	19.3
0.95	4.985	84.0	16.0
0.96	4.998	87.2	12.8
0.97	5.010	90.4	9.58
0.98	5.022	93.6	6.37
0.99	5.035	96.8	3.18
1.00	5.047	100.0	0

* This table has been further modified by Cathcart and Cuthbertson, see J. Physiol., 1931, 72, 349.

lated for respiratory quotients ranging from 0.707 to 1.0. These so-called *non-protein respiratory quotients* were obtained by determining the total oxygen consumption and carbon dioxide produced and then subtracting the volumes of these gases exchanged in the catabolism of protein. The quantity of protein undergoing catabolism is obtained from the urinary nitrogen, each gram

of the latter being equivalent to 6.25 grams of protein. In precise experiments upon heat production, the calories produced from the catabolism of protein as well as those derived from fat and carbohydrate would require to be determined. For example, a subject produces per hour 13.50 liters of carbon dioxide, consumes 16.00 liters of oxygen and excretes 0.5 gram of nitrogen in the urine. Now, each gram of urinary nitrogen represents the production of 4.76 liters of carbon dioxide and the consumption of 5.94 liters of oxygen.

Therefore:

the CO₂ produced by the subject in the catabolism of protein is $0.5 \times 4.76 = 2.38$ liters
the O₂ consumed in the catabolism of protein is $0.5 \times 5.94 = 2.97$ liters

Then:

the non-protein CO₂ production is $13.50 - 2.38 = 11.12$ liters
the non-protein O₂ consumption is $16.00 - 2.97 = 13.03$ liters
the non-protein respiratory quotient is $\frac{11.12}{13.03} = 0.85$.

It will be seen from table 39 that at this R.Q. the caloric equivalent of a liter of oxygen is 4.862. The heat produced by the combustion of non-protein materials is therefore, $13.03 \times 4.862 = 63.3$ Calories of which 50.7 per cent is derived from carbohydrate and 49.3 per cent from fat.

The heat production due to protein is $2.97 \times 4.485 = 13.3$ Calories. (The caloric equivalent of each gram of urinary N is 26.51, so, the heat production due to protein may also be obtained approximately by multiplying the figure for the urinary nitrogen (0.5) by 26.51.)

The total heat production per hour is therefore $63.3 + 13.3 = 76.6$ Calories. Of this, 42 per cent is derived from carbohydrate, 41 per cent from fat and 17 per cent from protein.

In ordinary determinations of the basal metabolic rate (p. 533) urinary nitrogen is not measured and the foregoing calculations are not undertaken; only a slight error is involved if the R.Q. is assumed to be 0.82 and the heat production taken directly from table 39.

(5) The isodynamic law

It was demonstrated by Rubner that just as the production of heat by a stove may be main-

tained at a constant level by burning different types of fuel, so in the generation of animal heat the different foodstuffs may replace one another in the diet in accordance with their heat producing values. Thus:—

- 100 grams of fat
- 232 grams of starch
- 234 grams of cane sugar
- 243 grams of dried meat

produce equivalent amounts of heat when ingested, i.e., they are isodynamic.

(6) Heat production in relation to surface area

TABLE 40

Showing relation of heat production per kilogram and per square meter of body surface in animals of different sizes

	WEIGHT	CALORIES	
		Per kilogram	Per square meter surface
	kgm.		
Pig.....	128.0	19.1	1,078
Man.....	64.3	32.1	1,042
Dog.....	15.2	51.5	1,039
Goose.....	3.5	66.7	967
Fowl.....	2.0	71.0	947
Mouse.....	0.018	654.0	1,188

The relatively low figures for the heat production of birds shown in the last column is due to their bodies containing a high proportion of osseous tissue which has an extremely low metabolism.

The heat produced by an individual at rest is proportional to the surface area of his body. Thus a fasting adult man and a starving dog, though the surface area of each and the total heat production were widely different, were shown by Rubner to give out in 24 hours closely similar amounts of heat per square meter of body surface, namely, 1134 and 1112 Calories respectively. A small animal, e.g., a mouse, therefore, since its surface area is greater in proportion to its mass, and since it generates the same amount of heat per unit of body surface, must obviously generate more heat per unit of body weight than a larger animal. The heat is produced in the tissues (muscles, liver, etc.); consequently these, in the case of the smaller animal, must be the seat of a much more active metabolism (see table 40).

(7) Physiological conditions which stimulate metabolism

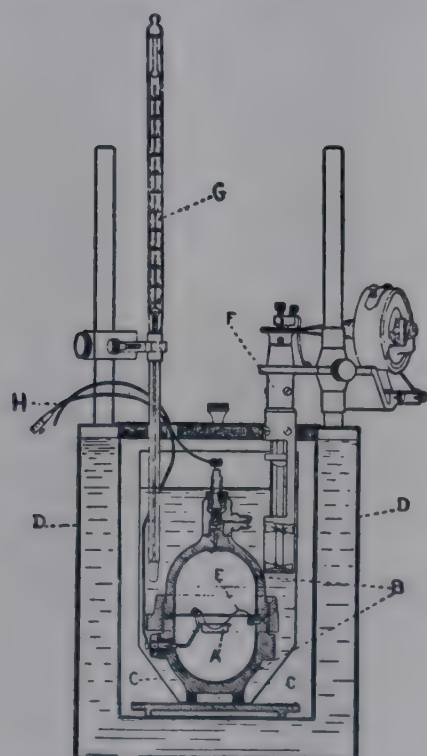
The heat production of the body is increased by (a) muscular work, (b) food, (c) a fall in

environmental temperature, or (d) a rise in body temperature (fever). These influences will be considered later.

CALORIMETRIC METHODS

THE BOMB CALORIMETER

The bomb calorimeter is employed for the determination of the potential energy of food. The food is dried and a weighed quantity ignited, by means of an electric fuse, in a hollow steel container lined with platinum and filled with pure oxygen (fig. 217). The heat evolved (energy of the food converted to heat) is absorbed by a



(Courtesy of the Emerson Apparatus Co., Boston, Massachusetts)

FIG. 217. Bomb calorimeter. A, platinum dish holding food sample; B, bomb filled with pure oxygen; C, vessel containing water, in which bomb is submerged; D, outer double-walled insulating jacket; E, fuse, which is ignited by an electric current; F, motor-driven water stirrer; G, thermometer; H, electric wires to send current through fuse. (After Rose.)

known quantity of water in which the container is immersed. The quantity of water in kilograms (plus the water equivalent of the apparatus) multiplied by the number of degrees centigrade through which its temperature has been raised gives, in Calories, the quantity of heat generated.²

² Another type of calorimeter called the *oxy-calorimeter* has been devised by Benedict. The caloric value of the food is determined by burning a sample in a special combustion chamber and measuring the *volume of oxygen* used. Knowing the caloric equivalent of a liter of oxygen used in the combustion of the three foods stuffs (p. 524) the heat value of the particular food sample is readily calculated. This method is really an adaptation of the method of indirect calorimetry used in the clinic and described on page 528.

CALORIMETRIC MEASUREMENTS IN ANIMALS AND MAN

An animal's energy is derived from the food which is to the body what fuel is to a furnace or machine. We have seen that the law of conservation of energy holds true for the animal body—that in a healthy animal which is maintaining a constant weight the intake and output of energy are equal. The food undergoes combustion in the tissues, its carbon being oxidized to carbon dioxide, its hydrogen to water and its potential energy converted into other forms of energy—mechanical, electrical, chemical and thermal. Thus the various processes of life are sustained. In a growing animal or in an animal during fattening the energy of the food is in part stored as new-formed tissue.

In the resting body all the energy liberated from the food ultimately appears as heat. A heat unit has therefore been chosen as the most convenient one for measuring and expressing the energy exchanges of the body. This unit is the *large calorie* (Calorie or Cal.), i.e., the quantity of heat required to raise the temperature of a kilogram of water 1 degree centigrade (actually from 15° to 16°C.). The Calorie used in physiological determinations is therefore 1000 times the *small calorie* (calorie or cal.) used in physical measurements.

Calorimetric methods are of two main types: (a) *direct* which is the same in principle as that described above for the bomb calorimeter, and (b) *indirect* in which the heat production is calculated from the respiratory exchanges.

Direct calorimetry

The elaborate nature of the apparatus required for this method precludes its use, especially for the human subject, in any ordinary laboratory or clinic. There are indeed only a very few in existence.

The apparatus consists of an insulated chamber large enough to accommodate an animal or a man. The heat eliminated from the body is absorbed by water circulating in coils of copper pipes. The temperature within the chamber is kept constant and the temperature of the subject is taken from time to time to ensure that heat is not being retained. The heat generated and radiated by the subject is absorbed by the circulating water. The temperature of this as it enters and leaves the chamber being known, and also its quantity (kilograms), the heat production in Calories can be determined. To this must be added the latent heat of the water vapor given off by the lungs and skin.

This, which amounts to about one-quarter of the total heat production, is calculated from the weight of the water in grams removed from the air by an absorber (sulphuric acid) multiplied by the factor 0.59 Calorie which is the latent heat of 1 gram of vaporized water at 20°C. A calorimeter of this type is usually combined with apparatus for determining the heat production by

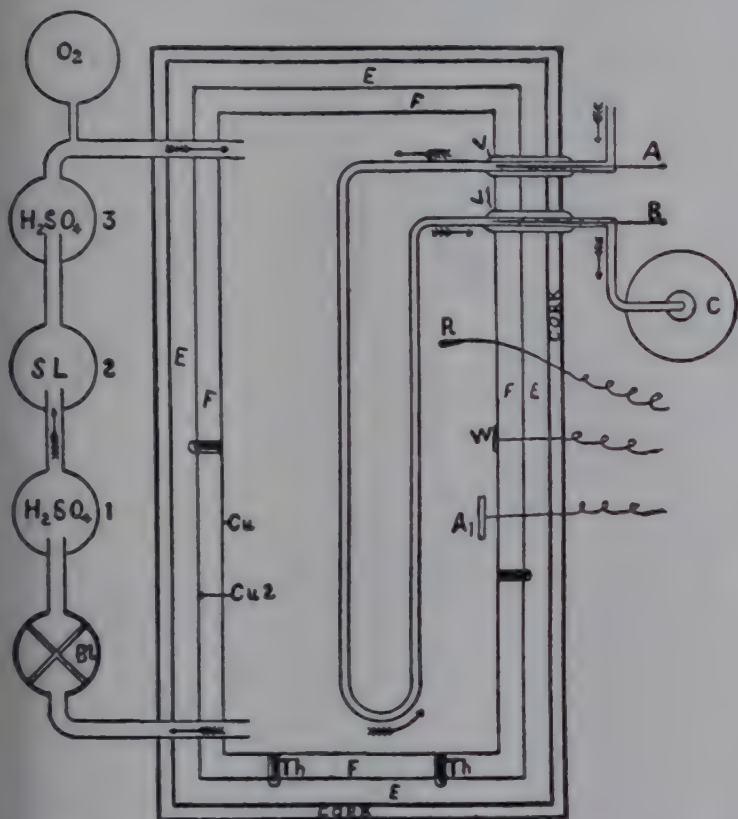


FIG. 218. Schematic diagram of the Atwater-Rosa-Benedict respiration calorimeter. Ventilating system: O_2 , oxygen introduced as consumed by subject; 3, H_2SO_4 to catch moisture given off by soda lime; 2, soda lime to remove CO_2 ; 1, H_2SO_4 , to remove moisture given off by patient; B1, blower to keep air in circulation. Indirect calorimetry: Increase in weight of H_2SO_4 (1) = water elimination of subject; increase in weight of soda lime (2) + increase in weight of H_2SO_4 (3) = CO_2 elimination; decrease in weight of oxygen tank = oxygen consumption of subject. Heat-absorbing system: A_1 , thermometer to record temperature of ingoing water; B, thermometer to record temperature of outgoing water; V, vacuum jacket; C, tank for weighing water which has passed through calorimeter each hour; W, thermometer for measuring temperature of wall; A_1 , thermometer for measuring temperature of the air; R, rectal thermometer for measuring temperature of subject. Direct calorimetry: Average difference of A and B \times liters of water + (gm. water eliminated \times 0.586) \pm (change in temperature of wall \times hydrothermal equivalent of box) \pm (change of temperature of body \times hydrothermal equivalent of body) = total calories produced. Th, thermocouple; Cu, inner copper wall; Cu_2 , outer copper wall; E, F, dead air-spaces. (After Lusk, *The Science of Nutrition*.)

indirect calorimetry as described below, the instrument being then referred to as a respiration calorimeter (fig. 218).

Indirect calorimetry: determination of the heat production from the respiratory exchanges

Experiments by several observers upon man and animals have shown that the results of

indirect calorimetry agree within less than 1 per cent with those obtained by the direct method. Two forms of apparatus—*closed-circuit* and the *open-circuit* or *air-current* types—are employed for indirect calorimetry. In the first mentioned method the subject rebreathes the air contained in a closed system; the carbon dioxide eliminated by the subject is removed by soda-lime and weighed; a measured volume of oxygen is supplied to replenish that which has been absorbed. In the open-circuit type, the subject inspires room air and expires into some form of container: the entire volume of expired air is measured and a sample analyzed for its carbon dioxide and oxygen percentages. Among the closed-circuit types of apparatus are those of Regnault and Reiset, and of Benedict and associates. The Douglas bag and Tissot methods are of the open-circuit type. In Haldane's method for small animals, though it is of the open-circuit or air-current type, the carbon dioxide is absorbed and weighed.

THE CLOSED-CIRCUIT METHODS:

In the Regnault-Reiset type of apparatus, the air is circulated through a closed system of which a chamber, large enough to accommodate the subject, forms a part. The air in the system is rebreathed repeatedly, carbon dioxide and water vapor being removed and oxygen supplied to replace that consumed. The air upon leaving the chamber enters first an absorbing vessel containing sulphuric acid which removes the moisture, then through a container filled with moist soda-lime which removes the carbon dioxide, and finally through a second sulphuric acid container which abstracts the water gained from the soda-lime. The dried and carbon dioxide-free air is then returned to the chamber. The quantity of carbon dioxide eliminated by the animal is given by the difference between the weights of the soda-lime container at the beginning and end of the experiment. Oxygen is run into the system from a cylinder and measured by means of a gas meter or by weighing the cylinder at the beginning and end of the experiment. The air in the chamber is analyzed at the end of the observation in order to ensure that no change in its composition has occurred. Only a few institutions on this continent, such as the Russell Sage Institute in New York and the Nutrition Laboratory at Washington, possess an apparatus of this type suitable for metabolic studies upon man. Such an apparatus was first constructed in America by Atwater and Rosa. It is usually combined with an apparatus of the direct type (fig. 218). The construction of a closed circuit type of apparatus for laboratory animals is not, however, such a difficult matter (fig. 219).

In other closed-circuit methods, such as the one described below, the subject is not enclosed

within a chamber; he simply breathes in and out of the apparatus through a connecting tube.

the closed system and both carbon dioxide elimination and oxygen usage were determined. In the

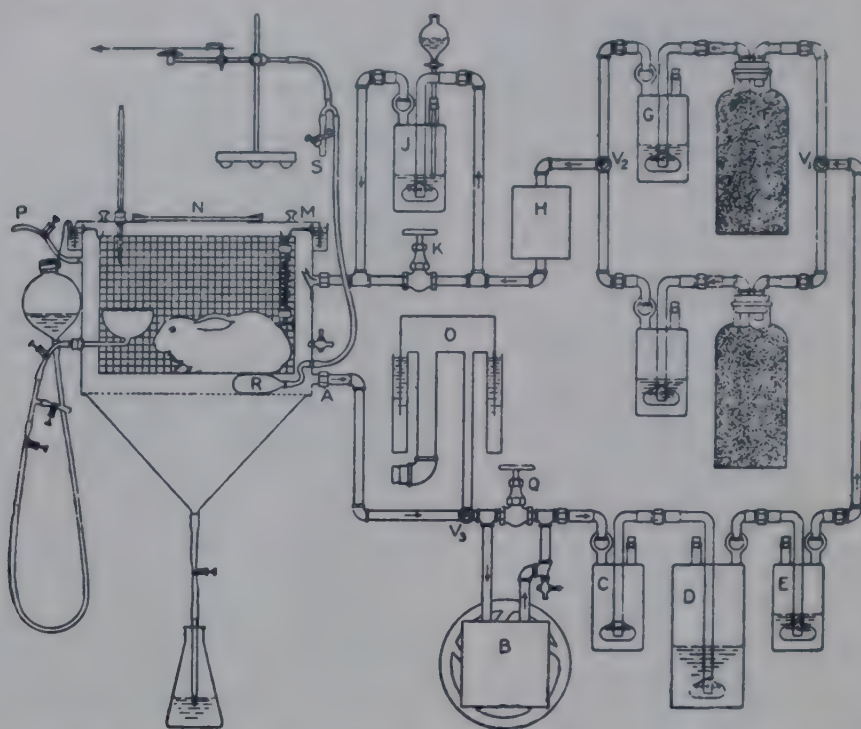


FIG. 219. Schematic outline of respiration apparatus for small animals. The air leaves the chamber at A and, after passing through the rotary blower B, which keeps the ventilating current in motion, is forced through the glass vessel C, which serves as a safety trap. The air then passes through the bottles C, D and E containing sulphuric acid to remove the moisture. The air, now water-free, but containing the CO_2 produced by the animal and lacking the O_2 which the animal has consumed, passes into the 2-way valve V_1 , where it may be deflected into the bottle F containing soda lime for the absorption of CO_2 . The moisture gained from the soda lime is absorbed by sulphuric acid in bottle G. The air then passes through a second 2-way tap V_2 to H containing dry sodium bicarbonate which removes the traces of acid vapor taken up by the air in passing through bottle G. J is a glass vessel containing water which supplies sufficient moisture to the air for the comfort of the animal. K is a by-pass valve. The chamber is constructed of copper and has a cover with a water seal M. N is a glass plate through which the animal can be observed. O is a spirometer attached to the system on the intake side of the rotary blower B. (From F. G. Benedict.)



FIG. 220. Benedict-Roth apparatus (courtesy of Warren E. Collins, Inc., Boston).

Clinical types of closed circuit apparatus In the earlier clinical types the subject was connected by means of a mouthpiece and flexible tubing to

type most commonly used today—the Benedict-Roth apparatus (figs. 220 and 221)—the heat production is calculated from the oxygen consumption alone. In order to purify the air the carbon dioxide is absorbed by soda-lime but the amount of this gas eliminated is not measured. In determining the basal metabolism (p. 533) the subject lies upon a couch and breathes in and out of the instrument through a mouthpiece and two wide-bore tubes (inspiratory and expiratory) provided with valves. The nose is clipped. The main part of the instrument consists of a bell-type spirometer. This is a hollow double-walled cylindrical vessel. In the narrow space between the two walls fits a second inverted hollow cylindrical vessel or bell. The bell is counterpoised so that it rides easily up or down in the annular space between the two walls. This space contains water which acts as a seal. At the commencement of the experiment, sufficient oxygen is admitted from an oxygen cylinder to raise a pointer on the spirometer bell to the zero mark upon an adjoined scale which has been calibrated to oxygen volumes. The breathing of the subject

through the inspiratory and expiratory tubes keeps the air circulating freely through the

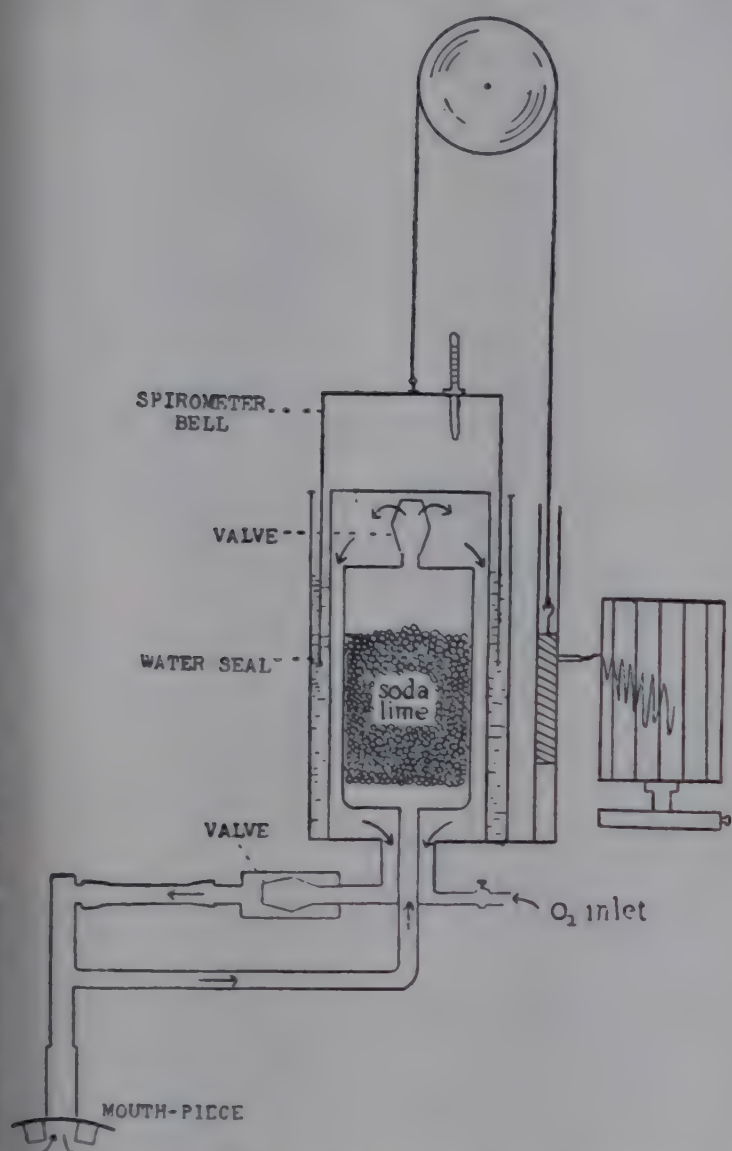


FIG. 221. Sectional view of Benedict-Roth closed circuit respiration apparatus.

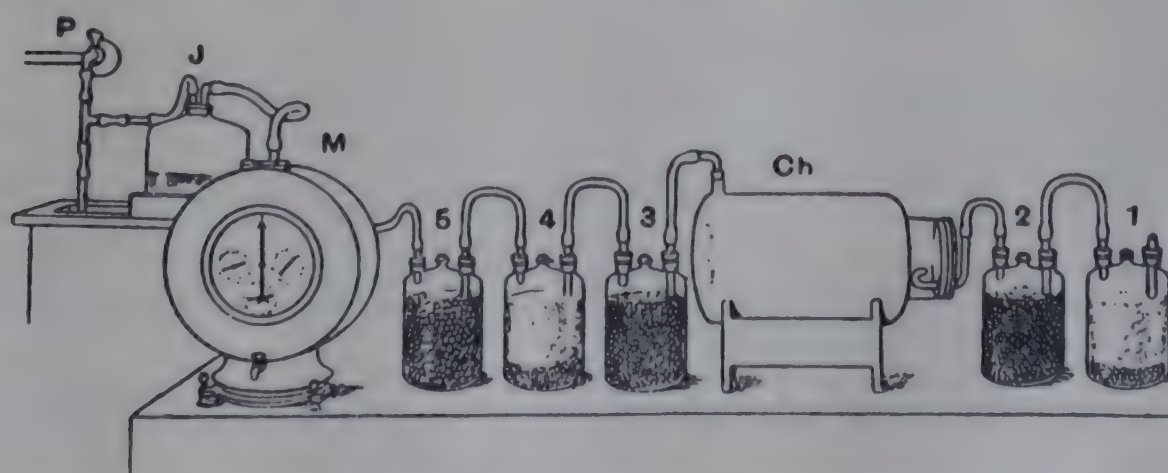


FIG. 222. Haldane's respiration apparatus. 1 and 4, soda lime; 2, 3 and 5, pumice stone soaked in sulphuric acid; Ch, animal chamber; M, meter. J is an inverted bell-jar standing in a trough of water, it serves to prevent sudden excess of negative pressure and to indicate the pressure actually employed. P, pump. (After Haldane.)

system. As oxygen is consumed the spirometer falls and from the difference in the levels of the pointer at the beginning and end of the experiment the oxygen usage is calculated. The volume of oxygen used, dry and reduced to standard temperature and pressure (see p. 531) is then

calculated. The heat production is found by reference to the table of respiratory quotients given on page 524. The average R.Q. in the postabsorptive state (see p. 533) is 0.82. Since the R.Q. of the subject is not determined by the foregoing method this value (0.82) is assumed. It will be seen from table 39 that at this R.Q. the caloric equivalent of 1 liter of oxygen is 4.825.

OPEN-CIRCUIT OR AIR-CURRENT METHODS:

In the *Haldane* type of calorimeter (which is suitable only for small animals, mice, rats or rabbits) a current of air is drawn through the system (fig. 222). Carbon dioxide and water are removed from the air before it enters the chamber and again after its exit therefrom. The carbon dioxide absorber on the outgoing current of air is weighed at the commencement and end of the experiment as in the Regnault-Reiset method, in order to obtain the quantity of carbon dioxide eliminated. The system with the exception of the first pair of absorbers and including the animal is then weighed. Since only oxygen has entered this part of the system (the air being CO_2 -free and dry) the gain in weight during the experiment gives the quantity of oxygen consumed by the animal.

The Douglas bag and Tissot methods (gasometric methods). In these methods the subject inspires atmospheric air and expires into a bag (Douglas method) or into a large bell-type spirometer (Tissot method). At the end of the experiment the total volume of expired air is measured and samples are analyzed for carbon dioxide and oxygen.

(a) *The Douglas-bag method.* The apparatus consists of a rubber-lined bag of from 60 to 100 liters capacity, a wide (20 mm.) flexible tube fitted with a flanged mouthpiece and a pair of rubber flutter valves similar to those used in gas masks. The valves are so arranged that the subject's inspired air is drawn from

the room while his expired air is directed into the bag (fig. 223, A). A three-way tap is situated at the junction of the bag with the tubing. In one position of the tap the subject can *expire* through the tubing into the outside air; breathing in this way for a short preliminary period enables him to become accustomed to the apparatus. At the commencement of the actual experiment the tap is turned so that the expired air enters the bag. At the end of the experiment the bag is closed by turning the tap back to the first position. The mouthpiece is then removed and the end of the flexible tubing connected with a gas-meter. A gas sampling tube is attached between the bag and the meter (fig. 223, B). The three-way tap is now opened and the bag compressed and finally rolled up in order to drive its

gas analysis apparatus, saturated with water vapor and its volume measured (fig. 225). It is then passed back and forth through the bulb containing potassium hydroxide solution which absorbs the carbon dioxide. It is then measured again. The difference between the two measurements gives the volume of carbon dioxide in the sample. Next, the oxygen is removed by passing the sample through a solution of potassium pyrogallate. The sample is measured a third time and the shrinkage in volume as shown by the difference between the second and third readings gives the quantity of oxygen absorbed. From the data

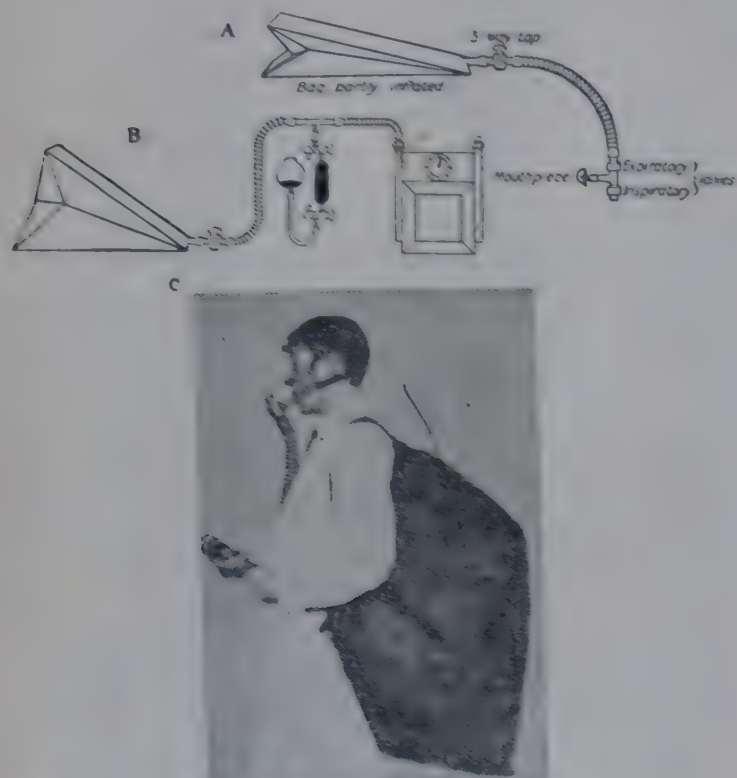


FIG. 223. Showing A, Douglas bag and tubing; B, Douglas bag with sampling bulb attached and gas meter for measuring the total volume of expired air (after Douglas and Priestley); C, subject equipped with Douglas bag apparatus during running or other types of muscular exercise. (After Hill.)

contents through the meter. During this procedure a specimen of expired air is taken for analysis. The Douglas method has the advantage that it can be employed for determining the metabolism during various types of muscular exercise, e.g. walking, running, etc. (fig. 223, C).

(b) *Tissot's method* is similar in principle to the foregoing. The subject expires into a large bell-type spirometer (capacity of 100 liters or more). The rise in the spirometer bell during the experiment is indicated by a pointer and scale. From this reading the total volume of expired air is derived. Samples of the latter are analyzed (fig. 224).

Gas analysis. The sample of expired air is drawn into the graduated burette of a Haldane

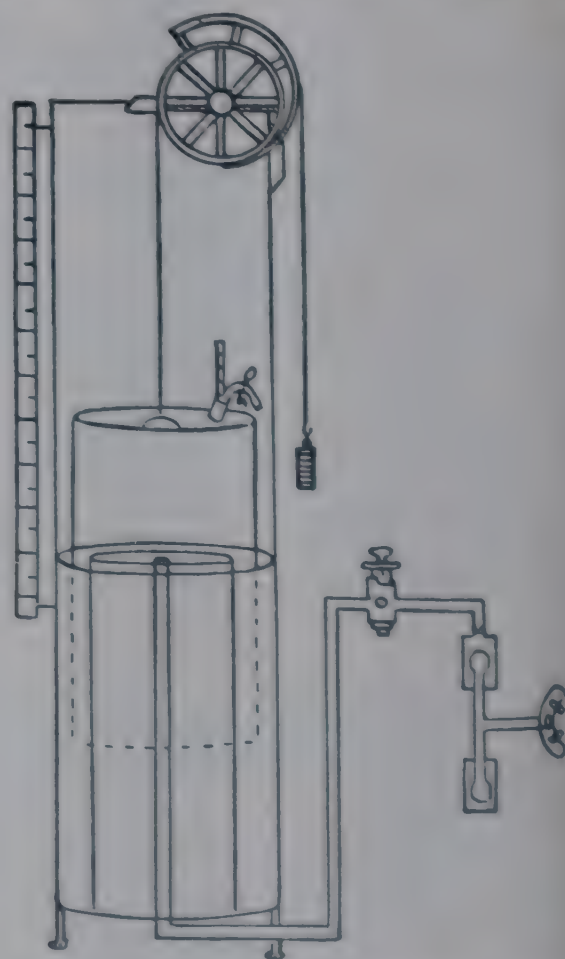


FIG. 224. Diagram of Tissot spirometer.

so obtained the percentages of carbon dioxide and oxygen in the sample of air are calculated.

Calculation of results. The following illustrates the steps in an actual metabolism experiment, using the Douglas or Tissot method.

Period of observation 10 minutes, barometer 750 mm. Hg.

Volume of expired air as read from meter (Douglas method) or as indicated by spirometer (Tissot method) = 70 liters.

Temperature of expired air (in meter or spirometer) = 20°C.

The volume of the gases must be reduced to standard conditions, namely, to 760 mm. Hg pressure and 273° absolute temperature (i.e., to 0°C.), and dry (i.e.,

the pressure of water vapor must be deducted from the barometer reading). The pressure of water vapor at 20°C. is 17.5 mm. So the corrected reading is;—

$$751.5 - 17.5 = 734.0 \text{ mm.}$$

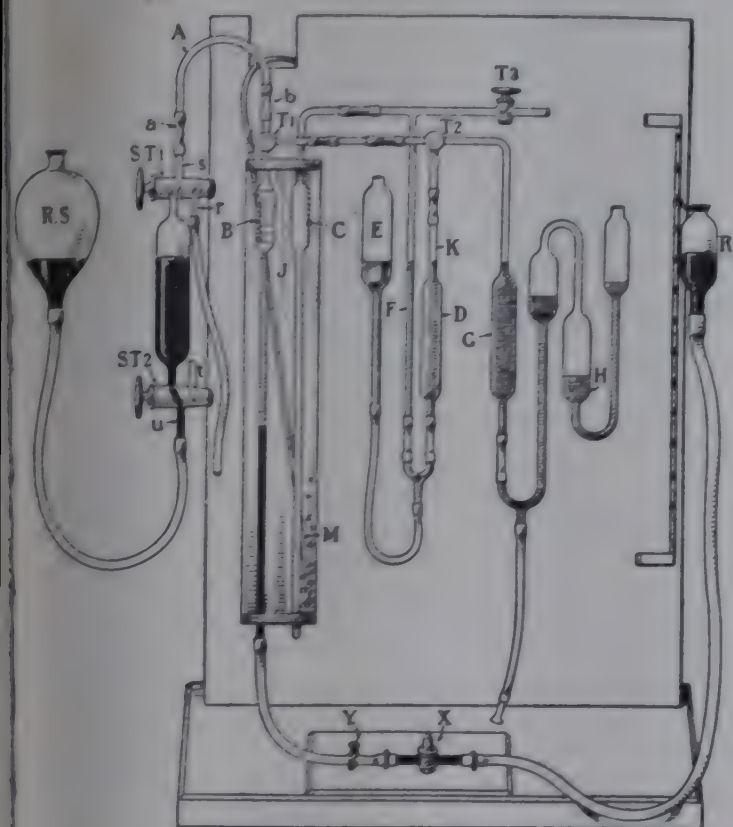


FIG. 225. Haldane gas analysis apparatus (small pattern) showing a gas sampler in position. A, glass tube connected to gas sampler; B, gas burette; C, control tube; D, caustic soda absorption pipette; E, caustic soda reservoir; F, caustic pressure tube; G, pyrogallol absorption pipette; H, caustic soda seal; J, water jacket; M, aeration tube; R, mercury reservoir; X, one-way tap to control movements of mercury; Y, screw clip for fine adjustments of pressure in K after the tap has been closed; R.S., mercury reservoir for gas sampler; S.T.1 and S.T.2, taps of gas sampler with double ports; r and t, side tubes by means of which when S.T.1 or S.T.2 are placed in position, the "dead spaces" of these taps and of the tube A can be filled with mercury; a, rubber connection, any air bubble in A may be expelled here as described in text; F, pressure tube for control; K, pressure tube for burette. Note T3 usually a three-way tap, placed at the junction of the vertical and horizontal tubes. (From Lamb, *An Introduction to Human Experimental Physiology*.)

the volume of the expired air at standard pressure and temperature (S. P. T.) and dry is therefore

$$70 \times \frac{734}{760} \times \frac{273}{273 + 20}$$

$\times 0.8993 = 62.95$ liters during the period of observation (10 minutes) or 6,295 cc. per minute

In practice these detailed calculations are avoided by reference to table 41 which gives the required factor by

which the observed volume is multiplied in order to reduce it to standard conditions and dry.

Results of gas analyses:

Expired air	Inspired air
CO ₂ = 3.50 per cent	CO ₂ = 0.04 per cent
O ₂ = 16.90 per cent	O ₂ = 20.93 per cent
N ₂ = 79.60 per cent	N ₂ = 79.03 per cent

Since the O₂ percentages in expired and inspired airs are 16.90 and 20.93 respectively it might be thought that 20.93 - 16.90 would give the percentage of O₂ absorbed. It will be noticed, however, that the percentage of N₂ is higher in the expired than in the inspired air. Nitrogen is inert insofar as respiration is concerned, being neither produced nor retained in the body, i.e., its absolute amount is not altered. Therefore, its greater proportion in the expired air can only mean that the volume of the inspired air (which of course was not measured) must have been greater than that of the dry expired air. So then, the volume of O₂ inspired must also have been greater than appeared from the analysis of the expired air. The cause of the discrepancy is that part of the absorbed oxygen has combined with hydrogen and in other ways, and so has not appeared as CO₂. The extent to which the O₂ in the inspired air exceeds that shown by the analysis of the expired air is proportional to the increased percentage of N₂ in the latter. Instead of the inspired air having contained 20.93 volumes of O₂ for every 100 volumes of air expired, it must have contained

$$20.93 \times \frac{79.60}{79.03}, \text{ or } 0.265 \text{ (a constant factor)} \times$$

$$79.60 = 21.09 \text{ volumes.}$$

Therefore the O₂ absorption is

$$\frac{21.09 - 16.90}{100} \times 6295 = 264 \text{ c.c. per minute.}$$

The calculation is abbreviated by the use of table 42.

The quantity of CO₂ produced may be calculated without correction since its percentage in the inspired air is negligible. Hence:

$$\frac{3.50 - 0.04}{100} \times 6295 = 218 \text{ c.c. per minute.}$$

The respiratory quotient is therefore

$$\frac{\text{Vol. CO}_2 \text{ expired } 218}{\text{Vol. O}_2 \text{ absorbed } 264} = .82$$

The caloric values of O₂ and CO₂ are given in, or can be calculated from table 39, p. 524. The heat production may be calculated from either of these values. For example, when the R. Q. is .82 the caloric value of 1000 cc. of O₂ is 4.825. Therefore, 264 cc. of O₂ represents a heat production of $4.825 \times \frac{264}{1000} = 1.27$ cal. per minute or 76.20 cal. per hour.

TABLE 41

Table for reduction to 0°C. and 760 mm. Hg and dry of 1 liter of air saturated with humidity, from 10° to 25°C., and 740 to 780 mm. (29.13 inches to 30.71 inches) of mercury
(Intermediate values may be obtained by interpolation)

BAROMETER

TEM- PERA- TURE	29.13 740	29.21 742	29.29 744	29.37 746	29.45 748	29.53 750	29.60 752	29.68 754	29.76 756	29.84 758	29.92 760	30.00 762	30.08 764	30.16 766	30.48 768	30.31 770	30.39 772	30.47 774	30.55 776	30.63 778	30.71 780	TEM- PERA- TURE
10	927.7	930.2	932.6	935.1	937.6	940.4	942.9	945.4	947.9	950.5	953.0	955.6	958.0	960.6	963.1	965.7	968.3	970.8	973.3	975.9	978.4	10
11	923.6	926.1	928.5	931.0	933.5	936.3	938.8	941.3	943.8	946.4	948.9	951.5	953.9	956.5	959.0	961.6	964.1	966.6	969.1	971.9	974.2	11
12	919.5	921.8	924.2	926.7	929.3	931.8	934.3	936.8	939.4	942.0	944.4	947.0	949.4	951.9	954.4	957.0	959.5	962.0	964.5	967.1	969.6	12
13	915.4	918.0	920.4	922.9	925.4	928.0	930.4	932.9	935.5	938.1	940.5	943.1	945.5	948.1	950.6	953.1	955.6	958.1	960.6	963.2	965.7	13
14	911.3	913.9	916.3	918.8	921.3	923.8	926.2	928.8	931.3	933.9	936.2	938.9	941.3	943.8	946.3	948.8	951.3	953.8	956.3	958.8	961.3	14
15	907.1	909.7	912.1	914.6	917.1	919.6	922.0	924.5	927.1	929.7	932.0	934.6	937.0	939.5	942.0	944.4	947.0	949.6	952.0	954.5	957.0	15
16	902.9	905.5	907.9	910.4	912.9	915.4	917.8	920.3	922.8	925.4	927.8	930.4	932.8	935.2	937.7	940.1	942.6	945.2	947.6	950.1	952.6	16
17	898.7	901.3	903.7	906.2	908.7	911.1	913.5	916.0	918.5	921.1	923.5	926.0	928.5	930.9	933.4	935.8	938.3	940.9	943.3	945.8	948.3	17
18	894.5	897.1	899.5	902.0	904.5	906.8	909.2	911.8	914.2	916.8	919.2	921.7	924.2	926.6	929.1	931.5	933.9	936.5	938.9	941.4	943.9	18
19	890.2	892.7	895.1	897.6	900.1	902.5	904.9	907.4	909.9	912.5	914.8	917.2	919.7	922.2	924.7	927.1	929.5	932.0	934.4	936.9	939.4	19
20	885.9	888.4	890.8	893.3	895.8	898.1	900.5	902.9	905.3	907.7	910.4	912.8	915.2	917.7	920.2	922.6	925.0	927.5	930.3	932.5	935.0	20
21	881.8	884.3	886.7	889.2	891.7	894.0	896.4	898.9	901.3	903.9	906.2	908.6	911.1	913.5	916.0	918.4	920.8	923.3	925.7	928.2	930.7	21
22	877.1	879.5	881.9	884.4	886.9	889.0	891.4	894.1	896.6	899.2	901.4	903.8	906.3	908.7	911.2	913.6	916.0	918.4	920.9	923.4	926.0	22
23	872.6	875.0	877.4	879.9	882.4	884.7	887.1	889.5	892.0	894.6	896.9	899.2	901.7	904.1	906.6	909.0	911.4	913.8	916.3	918.8	921.3	23
24	868.1	870.6	873.0	875.5	878.0	880.1	882.5	885.0	887.5	890.1	892.3	894.6	897.1	899.5	902.0	904.4	906.8	909.2	911.6	914.0	916.5	24
25	863.5	865.9	868.3	870.8	873.3	875.7	878.1	880.5	882.9	885.5	887.9	890.1	892.6	895.0	897.4	899.8	902.1	904.5	906.9	909.3	911.7	25

THE BASAL METABOLIC RATE (B.M.R.)

This is the term applied to the heat production of a subject who though awake is as nearly as possible at complete *muscular* and *mental rest*, and in the *postabsorptive* state (i.e., from 12 to 14 hours after a light meal when, it is assumed, the digestive processes are quiescent). The room temperature should be 20°C. For example, the prospective subject of a basal rate determination is directed to refrain from undue muscular exertion or fatiguing effort of any kind for 24 hours previously. A light meal with the minimum amount of protein is taken not later than 7 o'clock the night before the test which is undertaken at

TABLE 42

Volumes of oxygen in inspired air corresponding to 100 volumes of expired air with different percentages of nitrogen

PER CENT NITROGEN IN EXPIRED AIR	VOLUMES OF OXYGEN IN INSPIRED AIR	PER CENT NITROGEN IN EXPIRED AIR	VOLUMES OF OXYGEN IN INSPIRED AIR
78.5	20.80	79.6	21.09
78.6	20.83	79.7	21.12
78.7	20.85	79.8	21.14
78.8	20.88	79.9	21.17
78.9	20.91	80.0	21.20
79.0	20.93	80.1	21.22
79.1	20.96	80.2	21.25
79.2	20.99	80.3	21.28
79.3	21.01	80.4	21.30
79.4	21.04	80.5	21.33
79.5	21.07		

about 9 o'clock in the morning. For a period of 30 minutes or so before and during the test the subject should be lying down comfortably in a room with subdued lighting.

The apparatus most commonly employed for the determination of the basal metabolic rate in the clinic is the instrument of Benedict and Roth (p. 528). Tissot's method or the bag method of Douglas is also sometimes used.

BASAL METABOLIC RATE STANDARDS

We have seen that the metabolism is proportional to the body's surface area rather than to its weight (p. 525). For example, of two men of about the same age, one large and the other small, though the former has the greater total heat production, the heat production per unit of body surface is of practically the same value in both subjects. Consequently, since the surface area

of the larger man is, in proportion to his mass, less than that of the smaller, his heat production per unit of body weight must be less. In figure 226, A, are shown two wooden blocks. The volume and weight of the larger is some three times greater than that of the smaller, but its surface area is only twice as great. If the metabolic rate were accurately related to weight rather than to surface area, then of two similarly shaped animals differing in size to the same extent as the two blocks the metabolism of the larger would be three times greater than that of the smaller; it is found, however, to be only about twice as great.

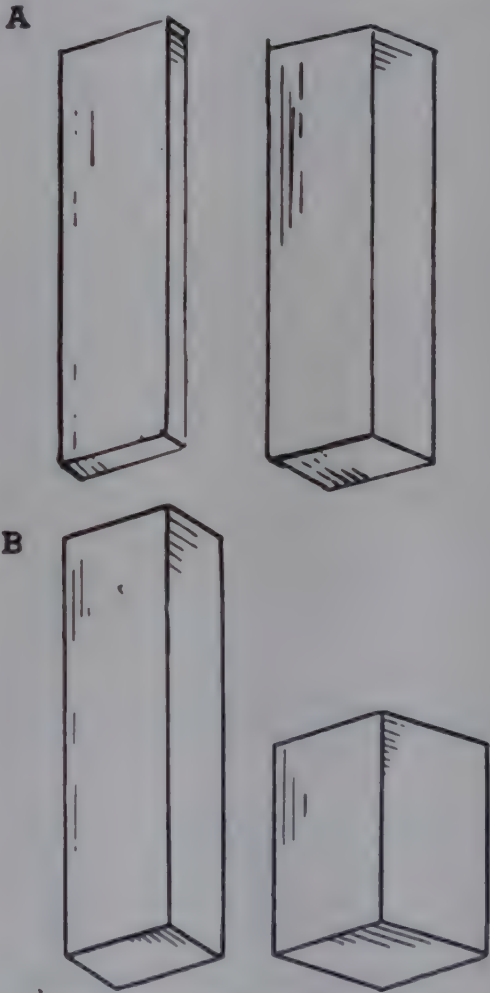


FIG. 226. Description in text.

Also two objects of the same volume and weight will have different surface areas if they differ in shape. In figure 226, B, the board and block are identical in volume and weight but the surface area of the former is more than double that of the latter. The nearer an object approaches in shape to a cube or a sphere the less is its surface area in proportion to its bulk. So, of two men of the same weight one tall and the other short and stout the former will have a higher metabolic rate. It is possible that this explains, in part at least, why a man of thin build often eats more than a stouter man of about the same weight. Since normal adults do not differ very greatly in size

and shape, it may be stated as a rough approximation that the heat production of the human body is a Calorie per kilogram per hour. But for the reasons just given it is much more accurate to express the basal metabolism in terms of body surface. Thus, the average basal rate of normal men between the ages of 20 and 50 years is from 38 to 40 Calories per square meter of body surface per hour. This value is constant for all normal men whether they are tall, short, thin or stout, large or small. Knowing a subject's height and weight his surface area can be determined at a glance from the chart (fig. 227), from the nomogram shown in figure 228, or from table 43; or it may be calculated from the height-weight formula.⁴ The average surface area for adults in Canada and the United States is about 1.6 square meters for women and 1.8 for men; the total basal

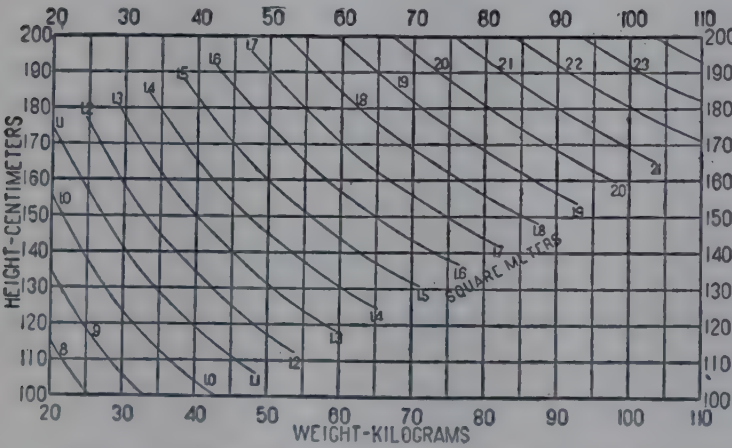


FIG. 227. Chart for determining surface area in man in square meters. (After Du Bois.) Example weight 60 kilograms, height 170 cm. = 1.70 sq. m.

heat production of the majority of normal adults ranges from 1400 to 1800 Calories per day.

The heat production per square meter of body surface is arrived at by dividing the value for the total heat production per hour of the subject, as determined by one of the methods already described (p. 529), by the figure for the surface area. For example, a man 175 cm. tall weighing 75 kg. has a surface area of 1.91 sq. meters. His total heat production is, say, 76.20 Calories per hour. His heat production per square meter per hour is therefore

$$\frac{76.20}{1.91} = 39.8 \text{ Calories}$$

⁴ The formula introduced by Meeh and modified by DuBois and DuBois is as follows:

$$A = W^{0.725} \times H^{0.725} \times 71.84 \text{ (a constant),}$$

where A = surface area in square centimeters, W = weight in kilogram, and H = height in centimeters.

Having obtained this figure it is customary to express the B.M.R. as normal or as a percentage above (+) or below (-) the normal. Thus, in the foregoing example the rate would be said to be normal. If it were 30 Calories per square meter per hour it would be expressed as -25 per cent and if 50 Calories as +25 per cent. The age and sex must also be considered since 39.8 Calories per square meter though normal for a full-grown man of 25 years or so would be above normal for

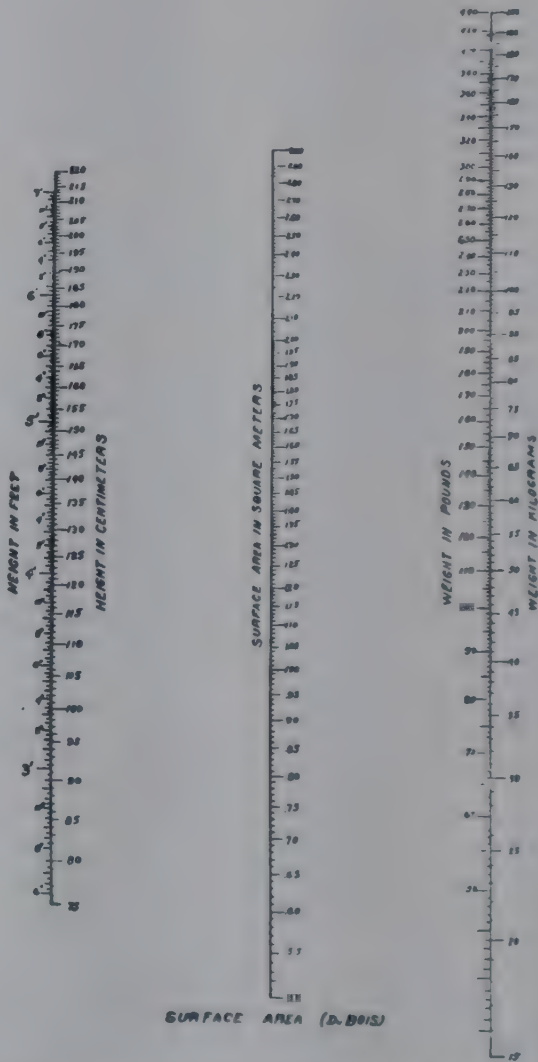


FIG. 228. Nomogram for surface area from weight and standing height, according to the formula of Du Bois. A line joining the weight and height of an individual crosses the scale of surface area at the required value. (After Boothby and Sandiford, from Du Bois, *Basal Metabolism*, Lea and Febiger. Philadelphia.)

a woman of the same age and below normal for a child (see below).

CONDITIONS WHICH INFLUENCE THE BASAL METABOLIC RATE

A. Physiological

(1) AGE AND SEX. The heat production per square meter of body surface diminishes progressively from infancy to old age being about 50 Cal. per square meter per hour at the age of ten or twelve and about 32 Cal. at 90 years

part completely oxidized, the nitrogen being excreted mainly as urea. The urine contains pyrimidines in insignificant quantities.

THE SYNTHESIS OF PURINES IN THE BODY

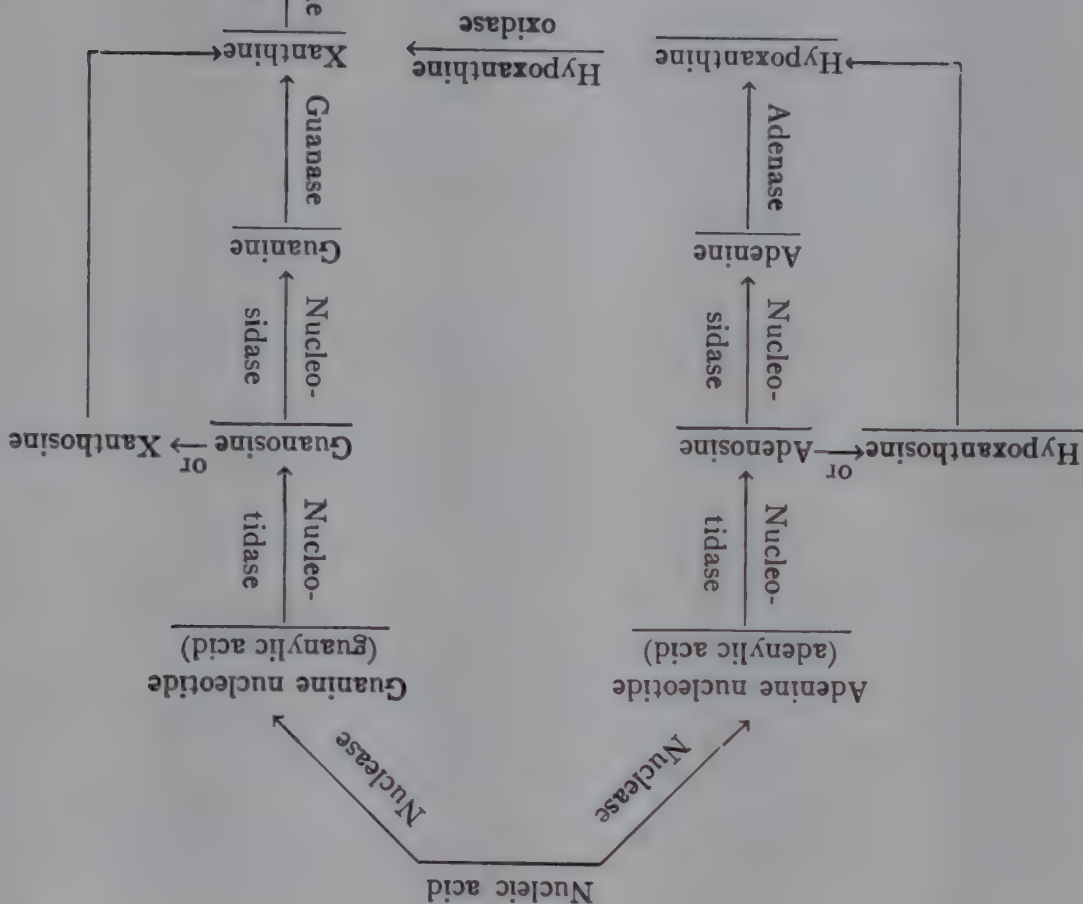
There is no doubt that purine synthesis occurs in the young mammal, for, when upon a diet comprised exclusively of milk, which is almost purine-free, it excretes uric acid or allantoin, and at the same time manufactures nucleic acid for the construction of cell nuclei. That synthesis also occurs in the adult was shown by Benedict, who kept a Dalmatian dog upon a purine-free diet for nearly a year, during which time the animal excreted 100 grams of uric acid. This had not apparently been derived from body tissue since the animal maintained a constant weight. The chief precursor of purines is histidine. A diet rich in this amino-acid increases the output of uric acid in the urine by over 30 per cent and is markedly decreased by a histidine-free diet.

THE PRODUCTION, DESTRUCTION AND EXCRETION OF URIC ACID

In man, uric acid is formed in part from purines taken in the food (*exogenous uric acid*) and in part from body purines (*endogenous uric acid*).

These animals would appear to possess an advantage over man, since allantoin is some 250 times more soluble than is uric acid. The conversion of uric acid to allantoin occurs in the liver (dog). Mann and his colleagues, for example, have shown that after hepatectomy uric acid accumulates in the blood, and when uric acid is injected, from 70 to 100 per cent can be recovered from the urine unchanged. This is in marked contrast to the behavior of the normal dog which excretes 98 to 100 per cent as allantoin. Extracts of dogs' liver are rich in uricase. The stages through which uric acid or allantoin is derived from nucleic acid are shown in the scheme below. The chemical changes involved in the conversion of guanine and adenine to uric acid or allantoin are indicated in the following formulae: (page 565).

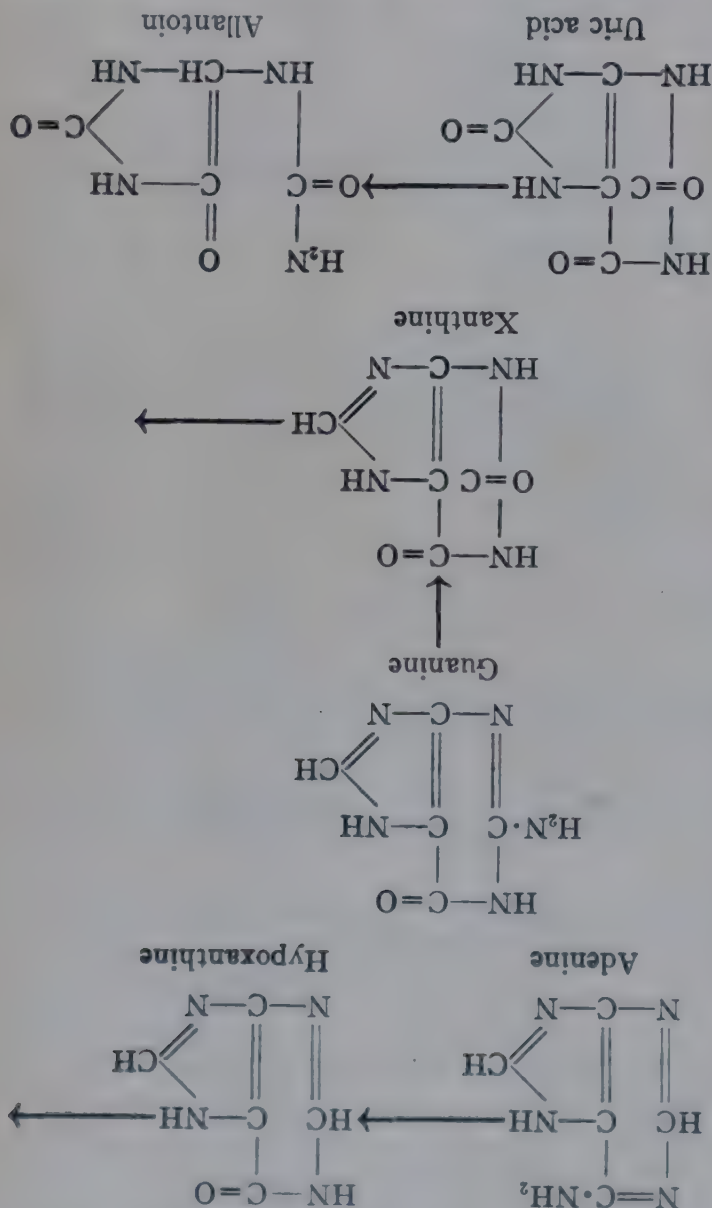
Little is known concerning the fate of the pyrimidines in man. In animals they are for the most part excreted as allantoin. The spotted coach-dog (Dalmatian) oddly enough is an exception: like man and unlike other canine breeds it excretes uric acid.



(man, ape, birds and reptiles)

(mammals other than man and apes)

by a specific tissue enzyme, *adenase* to form *hypoxanthine*. Hypoxanthine is then oxidized by the enzyme, *hypoxanthine oxidase*, to *xanthine* which in turn is oxidized, by means of *xanthine oxidase*, to uric acid. The other purine, *guanine*, is converted by the deaminative action of *guanine* to *xanthine* and by further oxidation to uric acid. In mammals other than the primates 80 to 98 per cent (depending upon the species) or the uric acid is oxidized further by an enzyme, *wricase*,



upon hydrolysis nucleic acid is split into its constituent nucleotides. The purine nucleotides are termed *adenylic acid* and *guanylic acid*, respectively. The further action of hydrolytic agents splits off phosphoric acid from the nucleotides. The residue (sugar + purine or pyrimidine) is then called a *nucleoside*. The adenine-containing nucleoside is known as *adenosine*; the one containing guanine is called *guanosine*.

Three mononucleotides occur in tissues uncombined: the nucleic acid molecule, i.e., separate from other nucleotides. These are not derived from cell nuclei but are probably in combination with the cytoplasm. They are, (a) *adenyl-pyrophosphoric acid* (*adenosinetriphosphate*) present in muscle (p. 615); it differs from the adenine-containing mononucleotide in thymus nucleic acid in that its sugar, as in plant nucleic acid, is d-ribose; it differs from the mono-nucleotide of both animal and plant nucleic acids in containing pyrophosphoric acid. (b) *Hypoxanthine* (*inosinic acid*) also found in muscle is formed by deamination of adenine in (a) and the removal of two molecules of phosphoric acid; its purine is hypoxanthine and its sugar is d-ribose. (c) *Guanylic acid*, constituted of phosphoric acid, d-ribose and guanine is found in various glandular tissues (e.g., pancreas).

THE END PRODUCTS OF PURINE AND PYRIMIDINE METABOLISM

Nucleoprotein is split into protein and nuclein by the action of pepsin. The nuclein is hydrolyzed into protein and nucleic acid by trypsin. The nucleic acid is quite resistant to the action of either of these enzymes, but is split into its constituent nucleotides by means of enzymes—*nucleases*—contained in the intestinal juice and the intestinal wall. Through the action of tissue enzymes the nucleotides undergo a series of changes. First, they are hydrolyzed by *nucleotidases* in the intestinal wall into phosphoric acid and the corresponding nucleoside (adenosine or guanosine). Each of the latter is split in turn by the action of a *nucleosidase* into its pentose and purine (adenine or guanine) components. Nucleosidases are present in the intestinal wall as well as in the general tissues. The purines give rise to uric acid (see scheme, p. 566).

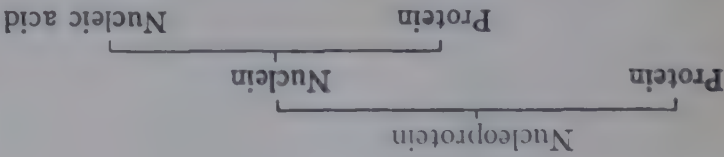
Uric Acid (first isolated by Steele in 1776 from urinary calculi). This urinary constituent is the end product of purine metabolism in man, higher apes, birds and reptiles. *Adenine* is deaminated in birds and reptiles uric acid is the end product of protein metabolism as well as of purine metabolism. According to Benedict from 60 to 70 per cent of the

urinary nitrogen of these species is in the form of uric acid. Of the intermediate stages in the production of uric acid from protein little is definitely known. According to Krebs and his associates, uric acid is synthesized in the bird's liver from ammonia, hypoxanthine being a primary product. The oxidation of hypoxanthine to xanthine is usually also attributed to xanthine oxidase; but according to Dakin, it is likely that a separate enzyme (hypoxanthine oxidase) is responsible for this change. The production of uric acid may follow another course, namely, conversion of the nucleoside adenosine or guanosine, by deamination, to hypoxanthine or xanthosine, which is then split into its pentose and purine groups, hypoxanthine or xanthine, respectively, (see plan on p. 566).

THE METABOLISM OF THE PURINE AND PYRIMIDINE BASES

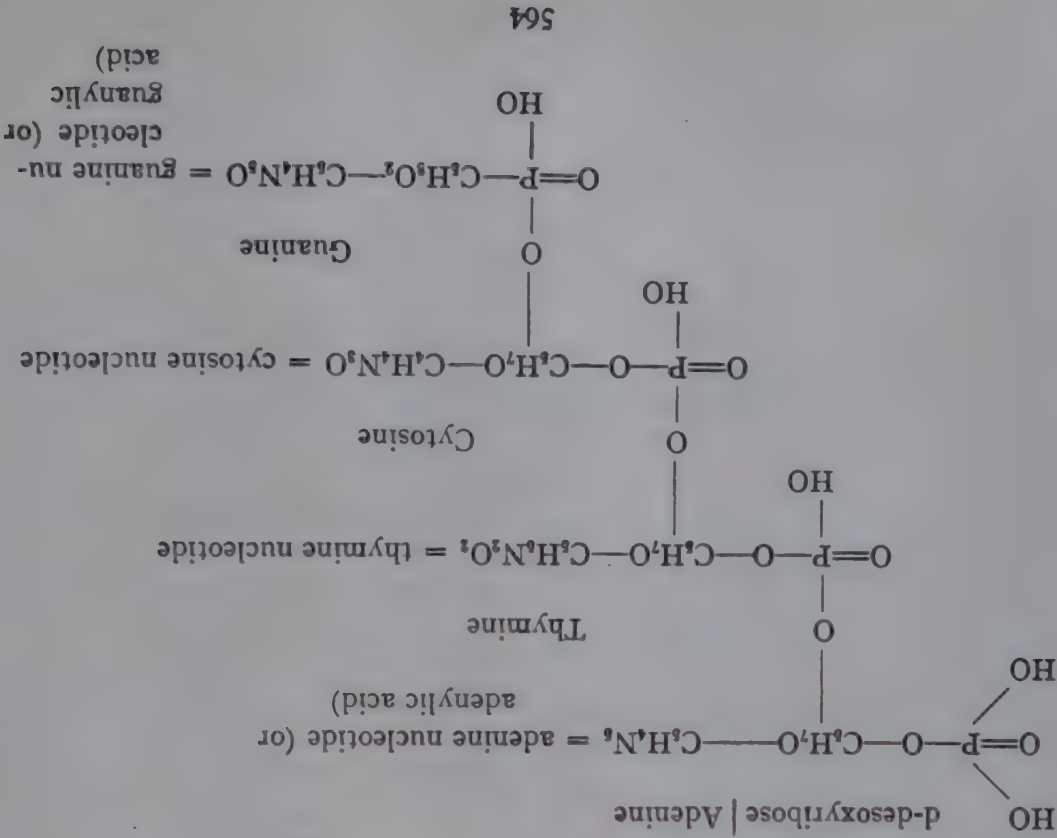
CHAPTER XLIX

One class of conjugated proteins—the *nucleo-proteins* (p. 539)—are compounds of simple basic proteins, *protamines* and *histones*, with *nucleic acid*. The protein is in salt-like combination with the acid but appears to be present in excess; when a nucleoprotein is hydrolyzed the excess is first split off leaving the substance called *nuclein*. This, upon further hydrolysis, yields protein and nucleic acid. Thus



Cell nuclei are composed largely of nucleoprotein; Miescher obtained this substance originally from pus cells and from the heads of the spermatozoa of salmon. There are two main varieties of nucleic acid. One is known as *thymus-nucleic acid*, the other as *yeast-nucleic acid*. They are also referred to as *animal nucleic acid* and *plant nucleic acid*, respectively. But thymus-nucleic acid is not, as it has been isolated from the nuclei of plant cells—rye embryos and yeast; plant nucleic acid was

Of the four mononucleotides in the nucleic acid molecule two contain each a purine base, and two each a pyrimidine base. The two purines are adenine ($C_5H_5N_9$) and guanine ($C_5H_5N_6O$). In thymus-nucleic acid the two pyrimidines are thymine ($C_5H_6N_2O_2$) and cytosine ($C_4H_5N_3O$). The sugar is *d-2-desoxyxyribose* ($C_5H_{10}O_4$), a 2-desoxyxypentose. Plant nucleic acid differs from the latter variety in that its sugar is *d-ribose* ($C_5H_{10}O_5$), and thymine is replaced by another pyrimidine—*uracil* ($C_4H_4N_2O_2$). Nucleic acids are therefore tetranucleotides. The following according to Levene is the structural formula of thymus nucleic acid.



instance, fed in any quantity, is inadequate for either growth or maintenance. Lactalbumin at a level of less than 8 or 9 per cent is incapable of promoting normal growth. Yet normal growth occurs on a diet containing 13.5 per cent zein and 4.5 per cent lactalbumin (fig. 230). The proportions of tryptophane and cystine and probably also of lysine are higher in lactalbumin than in body protein. Therefore, the excess of these amino-acids in lactalbumin, instead of being wasted, combines with the amino-acids of zein (which otherwise would be discarded) to form tissue protein.⁵

In a similar manner the amino-acids of gelatin are utilized if supplemented by a protein rich in tryptophane and cystine. Even two incomplete proteins, if one contains an abundance of the amino-acids which the other lacks supplement one another. So, the biological value of two proteins given together may be much greater than the sum of their values when fed alone. Proteins which lack the same amino-acid (e.g., casein and phaseolin which are deficient in cystine) cannot of course supplement one another. The supplementary relations of proteins is evident in the chief natural foods: these all contain two or more proteins (see table 54). For example, in milk, the deficiency of casein in cystine is made good by lactalbumin which contains a relatively high percentage of this amino-acid. Also, though gliadin of wheat will not support growth, wheat itself will. The lysin-poor gliadin is supplemented by the other wheat protein, glutenin, which is rich in lysine. Maize contains, besides zein, the supplementary protein glutenin. These facts, obviously, are of fundamental importance in dietetics, especially in the economy of agricultural feeding. Cheaper foods can be fed and good nutrition promoted if due consideration be given to the supplementary relations of their contained proteins. Gelatin rich in lysine improves the nutritional value of wheat and oats, both relatively poor in this amino-acid. There is also a pronounced supplementary relation between the proteins of milk and those of oats and wheat.

⁵ It follows that a protein of high biological value, i.e., one which possesses an assortment of amino-acids closely resembling that in body protein, i.e., one which when fed alone shows little wastage of nitrogen, will have little supplementing effect.

some samples of very fibrous beef, for instance, may be little higher than that of white flour.

THE SUPPLEMENTARY RELATIONS AMONG PROTEINS

It does not necessarily follow that because a certain protein is inadequate for growth or even

TABLE 54*
Character of proteins in some common foods

FOOD MATERIALS	CHIEF KINDS OF PROTEIN PRESENT	COMPLETE OR INCOMPLETE
Nuts	Excelsin	Complete
Cheese	Casein	Complete (low in cystine)
	Lactalbumin	Complete
	Glutenin	Complete
Wheat	Zein	Incomplete (lacks lysine and tryptophane, low in cystine)
Eggs	Ovalbumin	Complete
	Ovotellin	Complete
Gelatin	Gelatin	Incomplete (lacks tryptophane and tyrosine; only a trace of cystine, high in lysine)
Lean meat	Albumin	Complete
	Myosin	Complete
	Casein	Complete (low in cystine)
Milk	Lactalbumin	Complete
Navy beans	Phaseolin	Incomplete (low in cystine)
Peas	Legumin	Incomplete (low in cystine)
Soy beans	Glycinin	Complete
	Legumelin	Incomplete
	Gliadin	Incomplete (lacks lysine)
Wheat	Glutenin	Complete

* From M. S. Rose, "Foundations of Nutrition."

for maintenance that it is worthless in nutrition. It is evident from what has been said in the preceding paragraphs that an incomplete protein can be utilized if its shortcomings in one or more of the essential amino-acids are made good by the addition to the diet of some other protein, rich in the elements which the first one lacked. Zein, for

amino-acids which have been found indispensable for rats are also essential dietary constituents for other mammals, including man. There are, however, certain minor species differences, the growing mouse, for example, can dispense with arginine in the diet, since, apparently, it can synthesize this amino-acid in greater amounts than can the rat. Glycine, which is a dispensable amino-acid for mammals is an essential dietary component for chicks. The chick, also unlike the rat, has no

capable of maintaining nitrogenous equilibrium. The nitrogen balance could not be maintained upon a diet completely lacking in lysine, whereas, histidine proved to be dispensable. The relation of arginine to human nutrition is somewhat ambiguous. Holt and his colleagues found that nitrogenous equilibrium could be maintained for ten days upon an arginine-deficient diet. The seminal fluid of the subjects showed a reduction in the number of spermatozoa. When arginine was

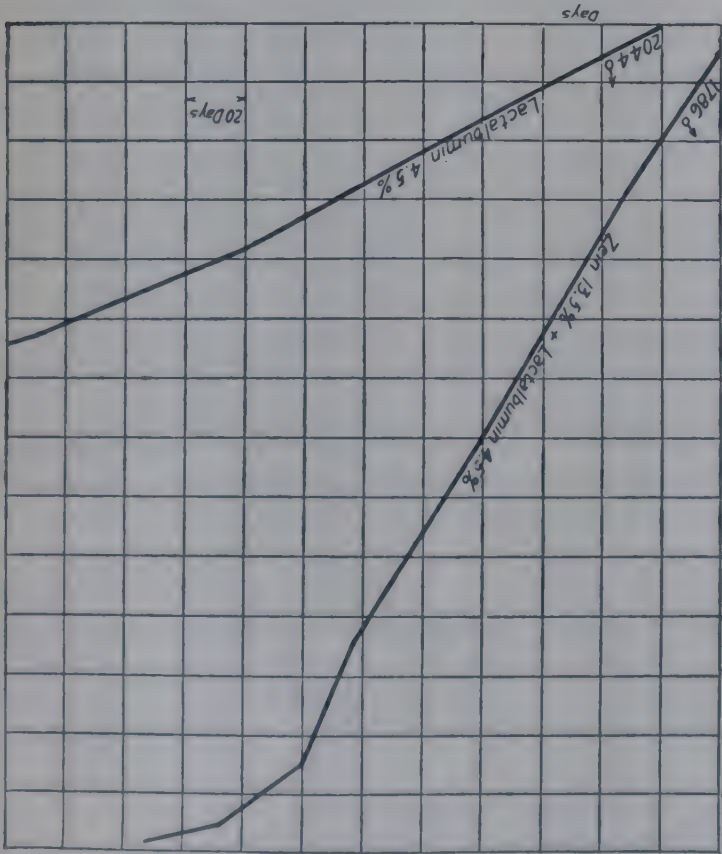
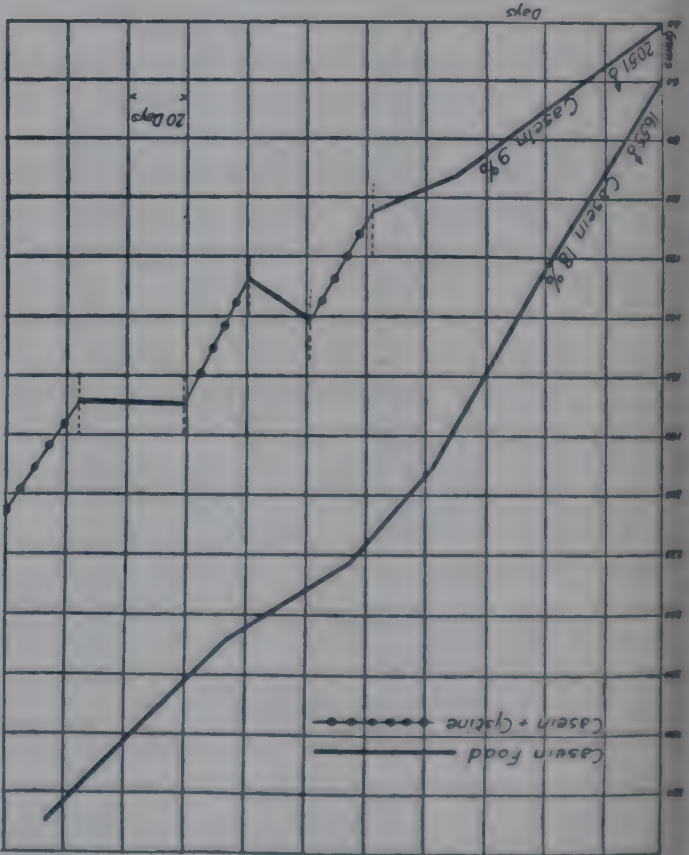


FIG. 230. Chart on left shows satisfactory growth of rat when 18 per cent of casein was present in the diet as the sole protein. With a smaller amount of casein—9 per cent—much less rapid growth ensued. That the insufficiency of the smaller amount of casein is essentially due to its relative deficiency in cystine is shown by the marked accelerating influence upon growth brought about by the addition of this amino-acid to the food containing 9 per cent of casein and the prompt retardation of growth which resulted from the withdrawal of cystine from the diet. Chart on right shows the favorable effect upon growth of supplementing a protein (zein), incapable of maintaining animals when it is the sole protein furnished in the diet, with a more "perfect" protein (lactalbumin). The portion of the lactalbumin used—4.5 per cent—was of itself insufficient for full growth. It evidently furnished the amino-acid groups which were lacking in zein. (After Mendel.)

ability to synthesize arginine. The essential or non-essential nature of a particular amino-acid, as well as the species differences, may possibly depend upon bacterial synthesis in the intestine. It has been found, for example, by Martin that rats fed a diet containing all the essential amino-acids fail to grow if succinylsulfazole is added to the food. The most suitable proteins for growth are those of animal origin and especially those which nature has provided for the nourishment of the growing animal, namely, lactalbumin (of milk)

added to the diet their number was restored to normal. These authors suggested that the degeneration of spermatozoa, which are very rich in arginine, furnished this amino-acid and thus permitted the nitrogen balance to be maintained. Tryptophane was found to be indispensable, the subjects developing negative nitrogen balances within a few days after having been placed upon a diet lacking in this amino-acid. Nitrogen equilibrium could not be maintained when valine, threonine, leucine, isoleucine or phenylalanine were lacking from the diet.

It seems that, generally speaking, the several

Tyrosine can be formed from phenylalanine. In rats deprived of *valine* grave nutritional defects develop which have been the subject of studies of Epstein and Rose. The animals become very sensitive to touch and show severe muscular incoordination, (e.g., staggering gait and circus movements) together with loss of appetite, emaciation and eventually death.

The amino-acid requirements for building new tissue (growth) are more exacting than those for repair (maintenance), i.e., for the maintenance of nitrogen equilibrium in the adult and the prevention of a loss of weight. Some amino-acids which

is added to the diet of which edestin is the sole protein, or cystine or methionine is added to the casein diet the other amino-acids in these proteins can be utilized and built into body tissue.⁴ Lysine is essential for maintenance as well as for growth, but for the former, relatively small quantities are required. Gliadin (of wheat), for example, which contains less than 1 per cent lysine is inadequate for growth even though fed in large quantities but is suitable as the sole source of protein in an adult. Zein, on the other hand, which is entirely lacking in lysine and contains little tryptophane is inadequate for either growth or maintenance. The

TABLE 53*

The amino acid content of a number of proteins

AMINO ACID		GELATIN	CASEIN	LACTALBUMIN	EGG ALBUMIN	GLIADIN	ZEIN	EDESTIN
Glycine.....	25.5	0.4	0.4	0.4	0.0	0.0	0.0	3.8
Alanine.....	8.7	1.8	2.4	2.2	2.0	2.0	9.8	3.6
Valine.....	0.0	7.9	3.3	2.5	3.3	3.3	1.9
Leucine isoleucine.....	7.1	9.7	14.0	10.7	6.6	6.6	25.0	20.9
Aspartic acid.....	3.4	4.1	9.3	6.2	0.8	0.8	1.8	10.2
Glutamic acid.....	5.8	21.8	12.9	13.3	43.7	43.7	31.3	19.2
Hydroxyglutamic acid.....	0.0	10.5	10.0	2.4	2.4	2.5
Serine.....	0.4	0.5	1.8	0.1	0.1	1.0	0.3
Proline.....	9.5	8.0	3.8	3.6	13.2	13.2	9.0	4.1
Hydroxyproline.....	14.1	0.2	0.0	2.0
Phenylalanine.....	1.4	3.9	1.2	5.1	2.3	2.3	7.6	3.1
Tyrosine.....	0.01	6.5	1.9	4.0	3.1	3.1	5.9	4.5
Cystine.....	0.17	0.3	4.0	0.9	2.4	2.4	0.8	1.0
Arginine.....	9.1	5.2	3.0	6.0	3.2	3.2	1.8	15.8
Histidine.....	0.9	2.6	1.5	2.3	2.1	2.1	1.2	2.1
Lysine.....	5.9	7.6	8.4	3.8	0.6	0.6	0.0	2.2
Tryptophane.....	0.0	2.2	2.7	1.3	0.8	0.8	0.17	1.5
Total.....	92.4	94.8	81.9	63.2	91.8	103.4	96.6

* Modified from Mitchell and Hamilton, "The Biochemistry of the Amino Acids," Am. Chem. Soc. Monograph Series No. 48, p. 191.

are essential for the growing animal can be dispensed with in the adult. Those necessary for both growth and maintenance are marked with an asterisk in the table on page 559. Even of these the level in the diet need not be as high for maintenance as for growth. The utilization of a protein deficient in one or other amino-acid is limited by that deficiency. For example, if edestin, which is poor in lysine, is the sole protein of the diet, the other amino-acids of which it is composed are utilized only in certain proportions limited by the lysine content. A large part of the remainder is discarded. Similarly the utilization of casein is limited by its methionine content. Now if lysine

Most of the work relating to the indispensability of the various amino-acids has been carried out upon rats. More recently, Holt and his colleagues have investigated this question in adult human subjects. Their results, in general, accord with those of animal experiments. Methionine, as the sole source of sulfur amino acids, was found to be

⁴ To make this point clear we may use as illustration the case of a type-setter who has lost a number of dies for, say, the letter A. He can continue to set type so long as his supply of A letters lasts, but when this is exhausted his work must cease though there is still a large number of other letters. His type-setting is limited by his supply of A letters.

supported. Also when the amino-acid deficiency is not too great, growth can be promoted by increasing the percentage of the incomplete protein in the diet (see table 53).

An essential or indispensable amino-acid is defined as one which cannot be synthesized in the body in adequate amounts for normal growth and nutrition and must therefore be supplied in the diet. Of the twenty-two amino-acids which have been identified as constituting protein material, eleven are indispensable for normal growth. They are as follows:²

- *Threonine [β -hydroxy- α -aminobutyric acid]
- *Valine
- Leucine
- *Isoleucine
- Arginine
- Lysine
- *Methionine
- *Phenylalanine
- *Tryptophane
- Histidine

Experiments in which it was shown that casein would not support growth unless fed in relatively large amounts or in smaller amounts and supplemented by cystine, led to the belief that this amino-acid was indispensable. The mistake was evidently the result of confusion with the other sulphur-containing amino-acid, methionine. The failure of growth on the low casein diet was due to this protein's inadequate methionine content, but this could be made good by the addition of cystine. In other words, cystine can substitute *in part* for methionine; cystine itself is not essential, for it can be *completely* replaced in the diet by methionine³ which can be converted to cystine in the body. Proof of the derivation of cystine from methionine was obtained by Tarver and Schmidt who fed animals methionine containing the radioactive isotope of sulphur (S^{35}) and later isolated isotopic cystine from their tissues. As mentioned of page 544, hemocystine combined with choline can, through transmethylation, substitute for methionine. *Arginine*, as mentioned on p. 545 can be synthesized in the body but not in adequate amounts for normal growth; it is therefore an essential constituent of the diet of young animals.

² Those marked with an asterisk are essential for both growth and maintenance.
³ An exception to this statement is concerned with the regeneration of plasma protein, for which (in dogs at any rate) cystine is essential; it cannot be replaced by methionine. Madden and associates).

and after the missing amino acid had been added to the diet. Rose's method consists in feeding a mixture of purified amino acids such as are found in casein. The effect upon growth was then determined after one or other amino acid had been omitted from the mixture.

THE ESSENTIAL IMPORTANCE OF CERTAIN AMINO-ACIDS FOR GROWTH AND MAINTENANCE

In 1907 Hopkins and Willcock found that when mice were fed upon a diet which contained zein (a protein of maize) as its sole protein, growth was arrested and the animals died in about 17 days. Zein is almost completely free from tryptophane. Yet, the addition of this amino-acid to the diet was not capable of promoting growth, and the survival period of the animals was extended to only 33 days. The addition of tyrosine was without effect since zein already contains this amino-acid in adequate amounts. It was shown by Osborne and Mendel that when lysine, which is completely lacking in zein, was added to the zein diet together with tryptophane, the animals grew

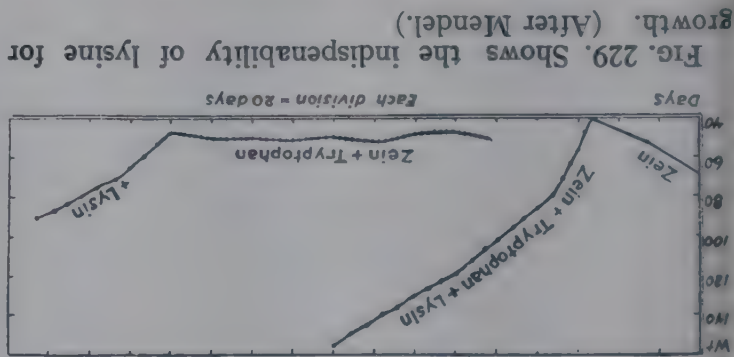


FIG. 229. Shows the indispensableity of lysine for growth. (After Mendel.)

normally and remained in good health (fig. 229). Lysine added alone was of no more benefit than tryptophane alone. *Gelatin*, like zein, is an incomplete protein. It lacks tyrosine and tryptophane and is very deficient in cystine. A diet which contains gelatin as its sole protein will not permit growth nor even maintain nitrogen equilibrium in an adult animal. When, however, the lacking amino-acids are added to the gelatin diet its defects are corrected.

Casein. Casein is deficient in glycine and has a low cystine content. If, however, casein be fed in sufficient quantity—about 18 per cent of the diet—or if cystine be added, normal growth results (fig. 230).

Edestin (a protein in hemp seed) is relatively poor in lysine as is also *gliadin* (of wheat) while *phaseolin* (of navy bean) is deficient in cystine and tryptophane. If these, or other incomplete proteins, are supplemented by adding to the diet the amino-acids in which they are deficient, growth is

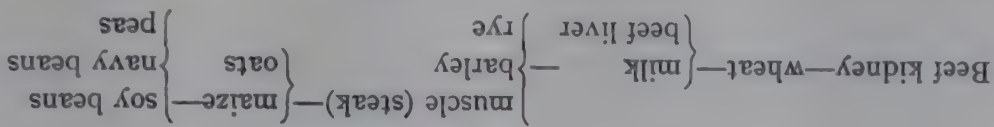
TABLE 52

Protein values of foods for maintenance and growth: Level of protein feeding, 8 to 10 per cent (After Mitchell and Hamilton)

FOOD	WATER CON-TENT*	PRO-TEIN CON-TENT* ON FRESH BASIS	Dige-ti-bility	Bio-logical value	META-BOLIC PROTEIN IN FECEST OF FOOD	PRO-TEIN VALUE ON FRESH BASIS
	per cent	per cent	per cent	per cent	per cent	per cent
Whole egg†	73.2	13.2	100	94	0.4	12.0
Milk	87.0	3.3	100	85	0.2	2.6
Egg white†	86.2	12.3	100	83	0.2	10.0
Beef liver	71.2	20.4	90	77	0.4	14.9
Beef kidney	76.7	16.6	99	77	0.3	12.3
Beef heart	62.6	16.0	100	74	0.5	11.3
Beef round	70.0	21.3	96	69	0.4	13.7
Pork ham	60.0	25.0	100	74	0.6	17.9
Veal§	73.4	20.7	100	52	0.4	12.4
Rollod oats	7.7	16.7	90	65	1.3	9.8
Whole wheat	11.4	13.8	91	67	1.3	7.1
White flour	12.8	10.8	100	52	1.3	4.3
Whole corn	10.3	7.5	95	60	1.3	3.0
Potato	78.3	2.2	78	67	0.3	0.8
Navy beans†	12.6	22.5	76	38	1.3	4.2

* Average analyses taken, as far as possible, from Bull. 28 (revised), Office of Experiment Stations, U. S. Dept. Agr.
† The metabolic nitrogen in the feces is assumed to equal 0.23 gram per 100 grams of dry matter of food. See Bull. Natl. Research Council, 1926, xi, pt. 1, no. 55, p. 23.
‡ Cooked.
§ The cut tested was not recorded. It proved to be very fibrous. Analysis for shoulder cut assumed.

tive value. Inferior proteins must be fed at higher levels. The relative values of several foods as given by these authors are shown below. The proteins of beef kidney head the list, the others are shown in order from left to right.



In order to know the value of a food as a source of suitable protein the quantity of protein which it contains as well as the latter's biological value must be considered. Thus a food may contain a poor protein in larger amounts or a first-class protein in small amounts. Again, in some foods the protein is both poor in quality and low in amount while in others both the quantity and quality of the protein are high. So we may take these two factors into consideration and speak of the *protein value* of a food. The quantity of protein in a sample of food is obtained by multiplying the value for its nitrogen content by 6.25 since pure animal food protein contains

was therefore $\left(\frac{40.1}{51.1} \times 100\right) = 79$ per cent.

A rat receiving a diet containing about 4 per cent of protein, ingested daily 56.9 mg. of nitrogen and excreted 27.6 mg. of nitrogen in the feces. Of the latter 21.7 mg. constituted metabolic nitrogen (p. 557). The unabsorbed N was therefore only (27.6 - 21.7 =) 5.9 mg., and the absorbed N (56.9 - 5.9 =) 51.0 mg. The daily urinary N was 48.6 mg. Of this, 37.7 was derived from the body tissues (estimated from urinary N on a nitrogen-free diet, p. 553). The total urinary nitrogen less this value for the endogenous nitrogen must represent the quantity of absorbed nitrogen which was excreted, that is, (48.6 - 37.7 =) 10.9 mg. is the quantity of absorbed nitrogen which had been wasted in metabolism. The absorbed nitrogen, as just stated, amounted to 51.0. So, (51.0 - 10.9 =) 40.1 mg. were retained in the body. The biological value of the dietary protein was therefore $\left(\frac{40.1}{51.1} \times 100\right) = 79$ per cent.

A method by which the nutritive value of a protein may be given numerical expression is employed by Mitchell. In this method, the value of the protein for repair (maintenance) or building of new tissue (growth) is given as a percentage of its *absorbed* nitrogen which is not lost in the urine, i.e., the percentage retained in the body. This is called its *biological value*. The animal is placed upon a basal diet complete so far as non-protein factors are concerned. In order that none of the protein shall be burned for energy purposes, the level in the diet is kept low, i.e., there should be no excess over that required for growth or maintenance. The following example from Mitchell will serve for illustration.

A rat receiving a diet containing about 4 per cent of protein, ingested daily 56.9 mg. of nitrogen and excreted 27.6 mg. of nitrogen in the feces. Of the latter 21.7 mg. constituted metabolic nitrogen (p. 557). The unabsorbed N was therefore only (27.6 - 21.7 =) 5.9 mg., and the absorbed N (56.9 - 5.9 =) 51.0 mg. The daily urinary N was 48.6 mg. Of this, 37.7 was derived from the body tissues (estimated from urinary N on a nitrogen-free diet, p. 553). The total urinary nitrogen less this value for the endogenous nitrogen must represent the quantity of absorbed nitrogen which was excreted, that is, (48.6 - 37.7 =) 10.9 mg. is the quantity of absorbed nitrogen which had been wasted in metabolism. The absorbed nitrogen, as just stated, amounted to 51.0. So, (51.0 - 10.9 =) 40.1 mg. were retained in the body. The biological value of the dietary protein was therefore $\left(\frac{40.1}{51.1} \times 100\right) = 79$ per cent.

In order to know the value of a food as a source of suitable protein the quantity of protein which it contains as well as the latter's biological value must be considered. Thus a food may contain a poor protein in larger amounts or a first-class protein in small amounts. Again, in some foods the protein is both poor in quality and low in amount while in others both the quantity and quality of the protein are high. So we may take these two factors into consideration and speak of the *protein value* of a food. The quantity of protein in a sample of food is obtained by multiplying the value for its nitrogen content by 6.25 since pure animal food protein contains

on an average 16 per cent of nitrogen. The use of this factor assumes, of course, that all the nitrogen in the food is protein nitrogen but, as mentioned in the footnote on page 557 a variable amount is present as non-protein nitrogen.

The value of individual amino acids were tested by Osborne and Mendel by feeding purified proteins known to be deficient in their amino acid constituents. Growth upon the deficient protein was observed before

It is rather surprising that wheat proteins stand so high; the results of other methods of investigation do not indicate such a superiority over the proteins of milk and beef, nor that barley and rye proteins are equal to those of beef muscle.

The determination of the minimal quantities of different proteins required for the maintenance of nitrogenous equilibrium in adult animals or of a positive balance (storage of nitrogen) in growing animals is also

That is, the wastage in digestion is 5 per cent or less. The digestibility of the proteins of nuts and fruits is low, that of the proteins of legumes and of potatoes is around 80 per cent (see table 52). The digestibility of wheat proteins is from 90 to 100 per cent thus approaching that for animal proteins.

(b) THE SUITABILITY OF A GIVEN PROTEIN FOR THE SYNTHESIS OF BODY PROTEIN. This depends upon the amino-acid constitution of the protein. It is obvious that the greater the proportion of amino-acids in the dietary protein which can serve for the construction of tissue protein, the greater will be protein's potential nutritive value. In other words, the more closely the amino-acid assortment in the food protein resembles that in body protein the less of the former need be furnished. A smaller proportion of the amino-acids will then be discarded to have their nitrogen eventually excreted in the urine, i.e., less of the food protein will be wasted.

Methods employed for estimating the nutritive values of proteins. Osborne and Mendel, employing rats, added a known amount of the protein to be tested, to a diet free from all other proteins, but adequate in other respects (i.e., one possessing the necessary energy value, minerals, and the vitamins then known). They expressed the nutritive value of the protein as the weight, in grams, gained by the animals per gram of protein fed, in the case of young rats (value for growth), or in the case of adult rats, the smallest quantity of the fed protein in grams, per gram of rat per week, necessary to maintain a constant body weight (value for maintenance). McCollum and associates also employed rats, feeding a basal diet of first class quality in all respects except that it lacked protein. The lack was made good by adding the protein to be tested, and the percentage of protein required to be added to the food mixture in order to promote normal nutrition gave an index of its nutritive value. The general state of nutrition of the animals, as indicated by rate of growth, fertility, care of young and longevity, was noted over a period corresponding to two-thirds or more of their life-span. On this basis, proteins were classed as "excellent," "good" or "poor." An excellent or first-class protein is one which "will support nearly optimum nutrition over periods approximating two-thirds or more of the normal life span of the rat when fed in amount corresponding to 9 per cent of the food-mixture." Nine per cent is therefore the critical level for a protein of the highest nutritive value.

Two factors must be considered in determining the nutritional value of a given protein: (a) its digestibility, i.e., the amount absorbed, and (b) its suitability for the construction of tissue protein.

(a) THE DIGESTIBILITY OF PROTEINS. Though by far the greater part of the nitrogen arising from the catabolism of amino-acids within the body is excreted in the urine, a small fraction is eliminated through the secretions of the digestive glands and intestinal mucosa. This, the so-called *metabolic nitrogen*, is estimated from the nitrogen of the feces upon a nitrogen-free diet. In a man it amounts to from 0.5 to 1.5 gram daily, varying in amount with the bulk (roughage) of the diet. In order, therefore, to determine the proportion of a given protein which has undergone digestion and absorption, the total nitrogen content of the ingested protein¹ is determined and from this value the nitrogen of the feces less that for the metabolic nitrogen is subtracted. Thus—

$$\text{Food N} - (\text{feces N} - \text{metabolic N}) = \text{absorbed N.}$$

The digestibility of the particular protein is then expressed as a percentage of the food nitrogen which has been absorbed into the blood. This percentage value is referred to as the *coefficient of digestibility*. For example, if the food contains, let us say, 10 grams of nitrogen and it is found that 9.5 grams have been absorbed the digestibility is 95 per cent. Digestibility in the sense just defined is quite different from the popular meaning of the term which refers rather to the subjective sensations accompanying digestion. Pork and veal, for example, are looked upon as indigestible types of meat, yet the percentage of their protein which is absorbed, i.e., their coefficient of digestibility, is high.

Proteins of animal origin have the highest digestibility which runs from 95 to 100 per cent.

¹ The total N in a sample of protein food is somewhat more than that actually present as protein-N. That is, a small part is present in the form of free amino-acids, their derivatives and other non-protein substances. Since much of the nitrogen in these forms is believed to be of definite nutritive value, no greater error is entailed in making the calculations upon the basis of the total food nitrogen than if a correction were made for their presence.

tion of urea, rather than the conversion of the deaminated residues to glucose is responsible for the specific dynamic action of protein. Lundsgaard found, for example, that though the administration of sodium acetate or sodium lactate was followed by only a slight increase in heat production, ammonium acetate or ammonium lactate caused a pronounced rise; even ammonium chloride caused a well marked increase in heat production.

The reactions responsible for the S.D.A. of protein are apparently situated in the liver and not in the tissue cells generally, since Wilhelmj, Bollman and Mann were unable to obtain any effect in hepatectomized dogs. Dock also found that after the administration of casein to rats the oxygen consumption of the hindquarters (muscular tissue) was 8 per cent greater than in the corresponding tissues of a control group, whereas the oxygen consumption of the abdominal viscera was 141 per cent greater.

The specific dynamic action of carbohydrate is thought to represent the energy liberated in excess of that required for the conversion of glucose to glycogen.

After a fast which depletes the glycogen stores, ingested glucose is oxidized in negligible amounts, yet it causes a pronounced specific dynamic action (Dann and Chambers).

The specific dynamic action of fat is ascribed to the increased concentration of fat in the tissue fluids and, as a consequence, to its more rapid oxidation ("plethora theory" of Lusk).

The glands of internal secretion appear to have no direct influence upon the S.D.A. of protein; the usual effect has been observed in a cretin with a basal metabolic rate 20 per cent below normal and it is not altered in hyperthyroidism. Thyroidectomy in animals is said, however, to reduce the S.D.A. of carbohydrate and fat. Cushing and Fulton found the S.D.A. of protein within the normal range in a number of cases of pituitary disease (hypopituitarism and acromegaly). Gaebler found it of normal value in hypophysectomized animals. In undernutrition the S.D.A. of all foods is increased. It is, according to some observers diminished in simple obesity (p. 609).

processes, i.e., to the contractions of smooth muscle of the alimentary canal or to the work entailed in the secretion of the digestive juices. This is proved by the following facts. Bones given to a dog, or agar agar, saline cathartics, water or meat extracts (which stimulate powerfully the gastric secretion) given to man, have no effect upon the heat production. Also, as already mentioned protein has no S.D.A. when new tissue is being laid down. On the other hand, the injection of certain amino-acids into the blood stream is followed by a specific dynamic effect.

The S.D.A. of protein has been shown to depend upon the following six amino-acids—*glycine*,

lowed by a specific dynamic effect. The S.D.A. of protein has been shown to depend upon the following six amino-acids—*glycine, alanine, leucine, glutamic acid, tyrosine and phenyl-alanine*. The last, as shown by Rapport and Beard, has the greatest effect of all. The action of glycine is greater than that of alanine but either of these exerts a smaller effect than tyrosine; the effect of leucine is slight. Until recently the specific dynamic effect of glutamic acid has been denied. The S.D.A. of a given quantity of meat equals that calculated from its content in these amino-acids. The other amino-acids investigated have no specific dynamic action.

The fundamental cause of the S.D.A. of protein is not altogether clear, though it is generally admitted that the amino-acids exert in some way a direct and specific stimulating effect upon the tissue cells, raising the latter's metabolism to a higher level, i.e., the combustion of the cells' own fuel material is increased. The extra heat is not due to the amino-acids themselves being utilized as fuel nor to the action of these materials in the unchanged state. It is in the intermediary reac-

tion of protein should be sought—possibly in the deamination process. Lusk suggests, however, that reactions involved in the conversion of the deaminated residues of the amino-acids to glucose and of glucose to glycogen are ultimately responsible for the extra heat production. These reactions are endothermic; in order to drive them, energy derived from an exothermic reaction is required. This energy is supplied by the oxidation of fuel materials by the tissue cells but an amount of energy is produced over that actually required. The excess appearing as heat constitutes the specific dynamic action. Since the R.Q. rises during the development of the S.D.A. the fuel undergoing combustion by the cells is thought to be glucose. These views have been criticized by Borsook and Winegarden who consider that from 25 to 60 per cent of the S.D.A. of protein results from the metabolism and excretion of nitrogen. The remainder of the heat production is attributed to the metabolism of carbon. There is a considerable body of evidence for the belief that the deamination of the amino-acids with the forma-

Calories respectively. The extra heat is generated by the combustion of body substance, so if loss of weight is to be prevented such an animal must be supplied with 130 Calories if his diet is protein; or if carbohydrates and fats are also consumed extra allowances must be made for the amounts of these substances which have been included. The extra heat resulting from protein food cannot be employed for the production of mechanical or other forms of energy. It is waste heat and is simply added to the heat produced by the muscular exertion. A diet very rich in protein is therefore unsuited to heavy muscular work. The S.D.A. of protein is an important factor, however, in the

The results of an experiment of Rapoport's which illustrates the utilization of the "waste heat" of the specific dynamic action of fat and glucose in exercise

TABLE 51

DEVIATION FROM (A)	EXCESS IN EXERCISE AND RECOVERY (PER KG.M. OF WORK)*	Calo-ries per hour	Calo-ries per hour	Calo-ries per hour	Calo-ries per hour
BEST-ING FROM (A) HOUR		12.7	15.2	15.4	17.8
DEVIATION FROM (A) HOUR		19.7	21.3	27.6	40.1
		2.40	2.54	3.38	3.48
		+5.8	-0.8	+40.8	+45.0

* Based on $\frac{1}{2}$ hour period after beginning of exercise.

regulation of body temperature (p. 629). With fat and carbohydrate the case is different, for the extra heat is harnessed in the performance of work. When exercise is undertaken upon either of these substances the heat due to their specific dynamic action is practically abolished, the extra energy being incorporated in the energy exchanges of the exercise (table 51).

When new tissue is being formed, i.e., when the nitrogen balance is positive, protein does not exert its usual specific dynamic action.

The cause of the specific dynamic action

Several explanations for the phenomenon have been offered. It is certainly not due to digestive

containing data from an experiment of Cathcart's illustrates this point.

Urine	7.78
1st day of starvation	7.43
1st day on cream (300 cc.), starch (400 grams)	3.58
2nd day on cream (300 cc.), starch (400 grams)	2.84
3rd day on cream (300 cc.), starch (400 grams)	
diet	

The nitrogen excretion upon a protein-sparing diet of this nature containing suitable proportions of carbohydrate and fat to meet the caloric requirements, represents the lowest level to which protein catabolism can be reduced. As just indicated, it is lower than the average excretion throughout a period of starvation. It is clear that none of the nitrogen excreted on the cream and starch diet shown in the foregoing table was derived from the breakdown of protein used for energy purposes since the necessary calories were supplied by carbohydrate and fat. The nitrogen excretion on such a protein-sparing diet is therefore an index of the inevitable disintegration of body protoplasm which occurs under ordinary physiological conditions. For this reason it was called, by Rubner, the "wear and tear" quota of protein metabolism. One of the lowest values reported for nitrogen excretion is that of Boothby and Sandiford, namely, 1.74 grams daily (0.024 gram per kilogram of body weight).

Carbohydrate exerts a specific sparing action quite apart from the fact that it furnishes energy and so relieves protein of the necessity of performing this duty, for the sparing effect exhibited by a given quantity of carbohydrate cannot be brought about by an amount of fat possessing double the caloric value. Carbohydrate when fed alone has a marked sparing action, whereas fat alone has little or no protein-sparing effect and a positive nitrogen balance cannot be established in man on a diet composed entirely of fat and protein. Nor will fat by itself, when given after a period of fasting, reduce the nitrogen excretion below that during the fast. Indeed, it actually increases the output of nitrogen. The increase may be related to the fact that fat, in the absence of carbohydrate, is incompletely oxidized; acetoacetic and β -hydroxybutyric acids appear and acidosis develops. A diet whose calories, up to 50 per cent or more, are derived from fat and the remainder from carbohydrate has, however, as great a protein-sparing action as one whose calories are derived from car-

bohydrate alone. Lactic and pyruvic acids, products of carbohydrate metabolism, are also protein-sparers to some extent. The sparing effect of carbohydrates can be demonstrated in the well-nourished animal as well as during starvation. When dogs in nitrogen equilibrium are given extra glucose, nitrogen is retained but the balance is established when the administration of glucose is stopped (Larson and Chaikoff). The difference between the sparing actions of fat and carbohydrate is not easily explained. According to one view (Landergeren) the specific sparing effect of carbohydrate depends upon the fact that glucose is vitally essential to the body and must be constantly supplied whatever the cost. If it is not available from outside sources or from the glycogen stores, tissue protein is broken down to yield materials from which it may be synthesized. Another more probable explanation of the peculiar sparing action of carbohydrate is, that it is used in the synthesis of the amino-acids which are incorporated into body proteins. According to this view the nitrogen resulting from the breakdown of tissue protein during fasting (or from tissue and food protein when the diet consists exclusively of protein and fat) is largely or entirely excreted. If, on the other hand, certain intermediary products of carbohydrate metabolism are available, e.g., pyruvic acid, etc., (p. 571) it is possible for amino-acids to be resynthesized. That is, nitrogen which would otherwise be wasted is retained.

THE SPECIFIC DYNAMIC ACTION OF FOOD

That the ingestion of food increases the heat production was known to Lavoisier. This effect of food in raising the metabolism above the basal level is called its specific dynamic action (S.D.A.). The heat production commences to rise within an hour after the food has been eaten, attains a maximum in about the third hour and is maintained at this level for several hours. The greatest specific dynamic action is excreted by protein food. When protein is fed alone to a fasting animal, in an amount possessing a heat value equivalent to the animal's basal metabolism, the heat production is raised 30 per cent or more above the basal level. Carbohydrate causes a rise of about 6 per cent and fat of 4 per cent. That is to say, when a quantity of protein, carbohydrate or fat having an energy value of 100 Calories is fed separately to an animal whose basal metabolism is 100 Calories daily, its actual heat production will be 130, 106 or 104

digest sufficient amounts of protein to satisfy his energy requirements. Under such circumstances he draws upon his stores of carbohydrates and fats, but after these have been exhausted the protein elements of his tissues are disrupted. The non-nitrogenous portions of the amino-acid molecules are burned to make up the calorie deficiency, and, as a consequence, quantities of nitrogen derived from food and body protein are excreted. It has been calculated that the human subject would have to consume, daily, some 8 pounds of meat—practically an impossible feat for a civilized man,—in order to furnish the necessary energy and maintain the body in nitrogen equilibrium. On the contrary, a carnivorous animal such as the dog which possesses a large capacity for the digestion of protein food⁶ thrives upon a diet composed entirely of lean meat. The Eskimos are also capable—according to Krogh—of consuming relatively enormous quantities of meat. On a mixed diet, as we shall see immediately, nitrogen equilibrium can be established on a very low protein intake.

PROTEIN SPARERS

Carbohydrates and fats are called *protein sparsers* since their presence in the diet relieves tissue protection of the necessity of furnishing energy. The nitrogen balance had been established, 350 grams of carbohydrate were withdrawn from the diet. The nitrogen excretion increased from 19.84 to 27.00 grams daily, the balance becoming negative. Also, the nitrogen excretion in the urine in starvation is nearly 3 times greater than that upon a diet, nitrogen-free, but of adequate energy value (i.e., one composed exclusively of fat and carbohydrate). The non-protein food has reduced the break-down of tissue protein. The following table

* The daily energy requirement of man is, say, 3000 Calories. Eight pounds of meat (3600 grams approximately) which is 20 per cent protein, has a caloric value of $\left(\frac{100}{20} \times 3600 \times 4.1\right) = 2900$. The energy expenditure of an average-sized dog, on the other hand, is around 600 Calories. It can consume in less than a minute 2 pounds (900 grams) yielding more than 700 Calories.

Example of adjustment of nitrogen balance to increased intake

TABLE 50*

established by simply feeding this quantity of protein nitrogen. It is found however that a considerably larger quantity is necessary. The reason for this is that the amino-acids are required by the body in different proportions from those present in the food protein. In order that the body shall obtain a sufficient quantity of suitable amino-acids for the replacement of its own protoplasm and for the manufacture of various secretions and other essential materials, a relatively large assortment must be available from which it can choose. Those not required are discarded. For this reason, equilibrium can be established upon a smaller quantity of animal protein, such as beef muscle which contains amino-acids more nearly in the same proportions as those in human body protein,

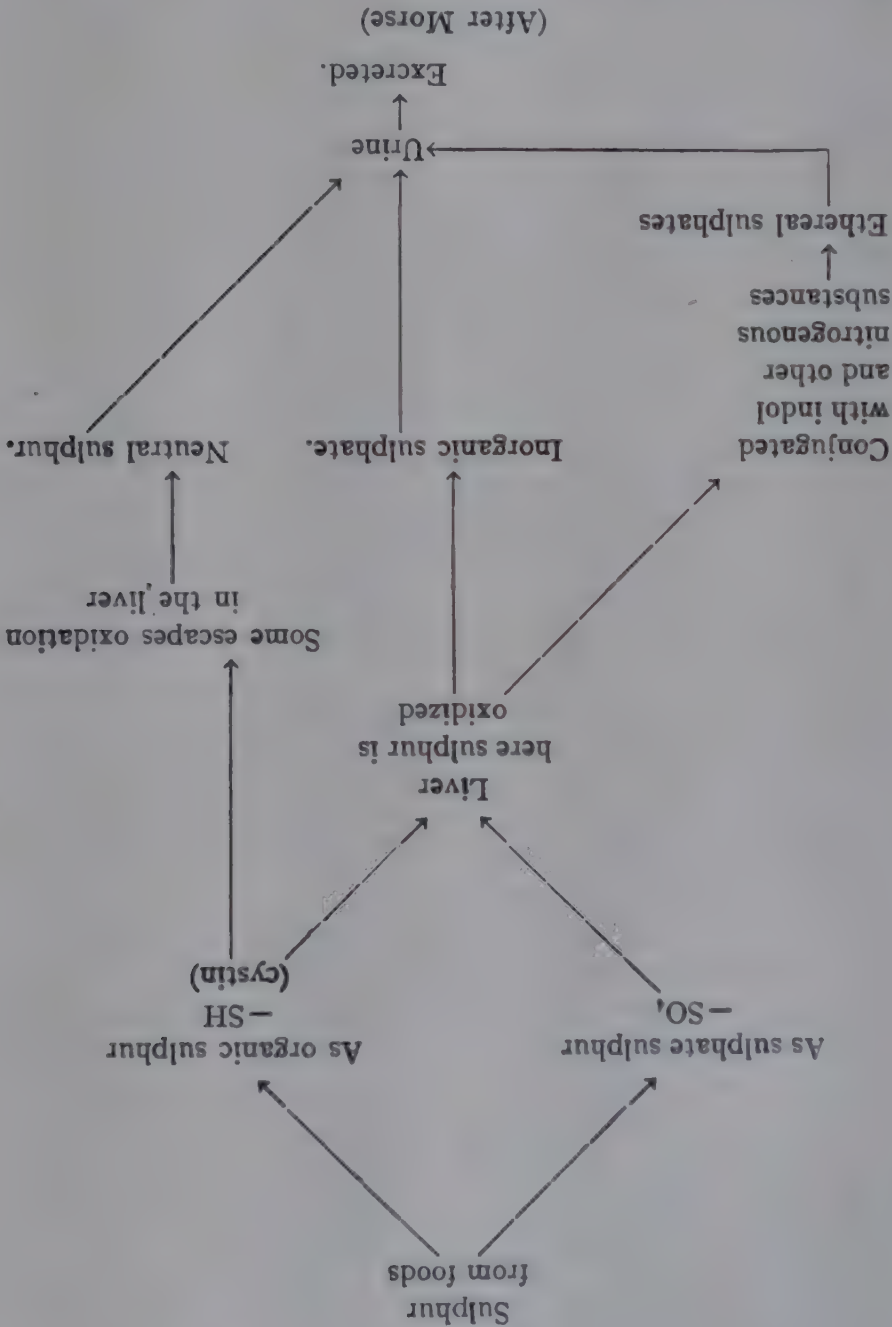
DAY	NITRO-GEN IN FOOD	NITRO-GEN IN FECES	NITROGEN "ABSORBED"	NITROGEN IN URINE	NITROGEN BALANCE
1	14.40	0.70	13.70	13.60	+0.10
2	14.40	0.70	13.70	13.80	-0.10
3	14.40	0.70	13.70	13.60	+0.10
4	20.96	0.82	20.14	16.80	+3.34
5	20.96	0.82	20.14	18.20	+1.94
6	20.96	0.82	20.14	19.50	+0.64
7	20.96	0.82	20.14	20.00	+0.14

* Modified from H. C. Sherman, "Chemistry of Food and Nutrition," 4th edition.

rather than upon vegetable proteins. The wastage of nitrogen is less in the former instance. If the only protein in the food is one entirely lacking in certain essential amino-acids (lysine, histidine, etc.) the loss of nitrogen resulting from the breakdown of such amino-acids in the body's protoplasm cannot be replaced. A negative balance results no matter how much of the inferior protein has been fed (see p. 557).
The quantity of protein required to establish nitrogen equilibrium depends very greatly upon the content of the diet in the other two food principles—fats and carbohydrates. It is impossible, for example, to establish nitrogen equilibrium in man upon an exclusively protein diet; the excretion of nitrogen always exceeds the intake even though the individual ingests protein to his full capacity. The reason for this is that man cannot consume and

sufficient amount of protein to repair this so-called "wear and tear" his output and intake of nitrogen will balance, i.e., he will be in nitrogen equilibrium. If his diet contains protein in excess of this amount the nitrogen not employed for repair is excreted and nitrogen equilibrium maintained. In starvation or on a low protein intake, on the other hand, the individual continues to excrete nitrogen derived from the dissolution of

the hair, sweat, saliva, etc., is negligible). The amounts of nitrogen excreted daily in the feces and urine, respectively, average 1.3 and 13 grams. The nitrogen of the feces is in part unabsorbed through the intestinal wall. When the intake and output are equal, the body is said to be in *nitrogen equilibrium*. When the intake exceeds the output the body is in *positive nitrogen balance*—nitrogen



his own protoplasm, and so goes into negative balance. In children, in adults recovering from wasting diseases or undergoing muscular training, and in pregnant women, the body, if the protein intake is liberal, does not excrete as much nitrogen as it receives. Nitrogen is retained for the manufacture of new tissue. The daily excretion of nitrogen of a man of average weight upon a nitrogen-free diet amounts to about 3 grams. It might be thought that nitrogen equilibrium could be re-

is being retained. If the reverse is the case, i.e., the output exceeds the intake, the balance is said to be *negative*—the body is losing nitrogen. When the nitrogen of the food is increased a greater quantity for a time thereafter is retained, but the balance soon becomes adjusted to the higher intake and gradually returns to its original value (table 50). The healthy adult requires protein to replace the inevitable loss of tissue protein. When given a

The quantities of inorganic and ethereal sulphates in the urine vary with the protein level of the diet; the neutral sulphur is influenced to a less degree. For this reason the two former partitions of the urinary sulphur were considered by Folin to represent food (exogenous) sulphur while the neutral sulphur was taken to be derived mainly from body protein (endogenous sulphur) (see p. 550). On a diet of meat or during prolonged starvation the ratio of sulphur to nitrogen in the urine is about 1 to 14, i.e., for every gram of sulphur there are approximately 14 grams of nitrogen. This is approximately the S:N ratio found in muscular tissue. A graphic summary of sulphur metabolism is shown on page 552.

As a result of the excessive production and absorption of putrefactive products the excretion of ethereal sulphates is increased in acute intestinal obstruction. They are also increased in carcinoma

TABLE 49

Concentrations of different forms of sulphur in whole blood and serum (After Denis)

SERUM	WHOLE BLOOD	
	per 100 cc.	mg.
	0.5-1.1	0.1-1.1
Inorganic sulphur.....	0.1-1.0	0.1-1.0
Ethereal sulphate sulphur.....	2.2-4.5	1.7-3.5

The inorganic sulphur of blood is elevated in renal insufficiency, intestinal obstruction and leukemia.

of the liver. Chronic constipation, however, exerts little or no influence upon the excretion of these substances (see p. 507).

The excretion of neutral sulphur is increased in the rare metabolic anomaly known as *cystinuria* and in cases of *melanotic sarcoma*, when an abnormal sulphur-containing pigment appears in the urine.

The non-protein sulphur of blood. The sulphur of blood, other than that present as a constituent of protein, amounts to from 3 to 5 mg. per 100 cc. The concentrations of the three forms is given in table 49.

AMMONIA (SEE PAGE 391)
NITROGEN BALANCES

The difference between the nitrogen taken in the food and that excreted in the feces and urine is spoken of as the nitrogen balance (that lost in

- (b) Glycoproteins, as mucosin-sulphuric acid in mucin and ovomucoid; and chondroitin-sulphuric acid in chondromucoid of cartilage (p. 939).
- (2) *Non-protein sulphur*
Sulpho-lipids
- B. *Inorganic*
Potassium, sodium and magnesium sulphates.

THE DISTRIBUTION OF SULPHUR IN THE BODY. Sulphur is contained in the ordinary tissue proteins; in hair, horn, feathers, etc.; in mucin, as mucosin-sulphuric acid and chondroitin-sulphuric acid; in certain glycoproteins of tendons, vitreous humor, cornea and connective tissues; in glutathione and insulin; in the taurocholic acid of bile; as sulphocyanate in saliva; in ergothioneine, a compound found in red corpuscles; in certain pigments (melanins, urochrome), and in nervous tissue as sulpholipoids. Inorganic sulphates are contained in the body fluids generally.

The loss of sulphur from the body occurs in the shedding of hair, nails, etc., in the bile, saliva and gastro-intestinal secretions. The great bulk of the sulphur loss, however, occurs through the kidneys.

The history of sulphur in the body. The sulphur liberated in the catabolism of dietary protein is largely converted to inorganic sulphates. A part of the inorganic sulphate derived from this and other sources becomes conjugated in the liver with substances produced in the intestine by the bacterial decomposition of protein to form *etheral sulphates* (p. 507). The latter are excreted in the urine. The products of bacterial action, among which are phenol derived from phenylalanine and tyrosine, and indole and skatole from tryptophane, possess toxic properties. Their excretion as etheral sulphates constitutes a detoxicating mechanism. When the detoxicating function of the liver is depressed as a result of hepatic disease, these toxic substances are excreted by the kidney in abnormal amounts in the free state.

Urinary sulphur. The total urinary sulphur is made up of the following:

- (1) Inorganic sulphur (85 to 90 per cent). Compounds of sulphuric acid with Na, K, Ca and NH₄.
- (2) *Ethereal sulphate sulphur* (6 to 8 per cent), e.g., potassium and sodium salts of indoxyl sulphuric acid. The latter is known as indican.
- (3) *Neutral sulphur* (4 to 6 per cent) e.g., sulphur-containing amino-acids, urochrome, thiosulphates, thiocyanates, taurocholic and oxyproteic acids.

is from 20 to 26 for the majority of normal men and from 14 to 22 for women. Its value depends upon the muscular development of the individual; the sex variation being due presumably to the different relative amounts of fatty and muscular tissues of male and female bodies. Athletic women for this reason have a coefficient as high as or higher than a man of obese build and poor muscular development.

TABLE 48
(After Folin)

NITROGEN-RICH DIET		NITROGEN-POOR DIET	
Volume of urine.....	1170 cc.	385 cc.	
Total nitrogen.....	16.8 grams	3.60 grams	
Urea nitrogen.....	14.70 grams	2.20 grams	
Ammonia nitrogen.....	0.49 gram = 3.0%	0.42 gram = 11.3%	
Uric acid nitrogen.....	0.18 gram = 1.1%	0.09 gram = 2.5%	
Creatinine nitrogen.....	0.58 gram = 3.6%	0.60 gram = 17.2%	
Undetermined nitrogen.....	0.85 gram = 4.9%	0.27 gram = 7.3%	
Total sulphur.....	3.64 grams	0.76 gram	
Inorganic SO ₄	3.27 grams = 90.0%	0.46 gram = 60.5%	
Ethereal SO ₄	0.19 gram = 5.2%	0.10 gram = 13.2%	
Neutral S.....	0.18 gram = 4.8%	0.20 gram = 26.3%	

THE METABOLISM OF SULPHUR

Sulphur enters the body mainly as a constituent of the amino-acids *cystine* and *methionine*. Food also contains inorganic sulphates, e.g., sodium and potassium sulphates, small amounts of sulphur in the form of sulpho-lipoids (sulphatides), and sulphur combined in certain glycoproteins as mucotin-sulphuric acid and chondroitin-sulphuric acid. Sulphur in inorganic form cannot be used in the construction of body protein. Practically speaking, the body is dependent for its sulphur supplies upon the two sulphur-containing amino-acids mentioned above. Food sulphur may be summarized as follows:

A. Organic
(1) Protein sulphur

(a) Sulphur-containing amino-acids, cystine and methionine.

generative changes occur in the muscles. The disease is accompanied by a high degree of creatinuria and a reduction in the excretion of creatinine. The thymus is frequently enlarged. Administered creatine is practically all excreted as such. Death results from involvement of the respiratory muscles. Very promising results have been reported following the treatment of this condition by the oral administration of glycine. Of 12 cases treated by Boothby with glycine and ephedrin, a drug which also has a favorable influence upon the disease, 10 were improved, and 4 of these markedly improved. Glycine apparently exerts no beneficial effect upon progressive muscular dystrophy. In 1934 Walker described a dramatic improvement in a case of myasthenia gravis produced by giving phosostigmine (eserine). More recently "Prostigmin" has been used in a series of cases with even more satisfactory results. The almost immediate improvement in the condition of the patients suggests that the drug acts specifically upon the neuromuscular mechanism attacked by the disease. The effects of one injection persist for eight hours or so. As discussed elsewhere (p. 946) the physiological effect of phosostigmine and presumably of "Prostigmin" is to inhibit the action of the esterase which is responsible for the destruction of acetylcholine liberated at certain nerve terminals, but the exact manner in which this agent exerts its beneficial effect in myasthenia gravis is unknown. In this disease the blood cholinesterase is not higher than the normal. On the other hand, a fall in the cholinesterase activity of the blood after prostigmine administration has been demonstrated. A delayed and more prolonged improvement in muscular power of these patients follows the injection of choline esters (acetylcholine and acetyl-β-methylcholine). Potassium is also reputed to exert a salutary effect.

Creatinine excretion as an index of muscle metabolism

The daily output of creatinine in the urine is constant for the individual, amounting to from 1.5 to 2.0 grams for men and from 0.8 to 1.5 grams for women. This corresponds to about 2 per cent of the creatine of the body. Unlike the excretion of urea, which is derived largely from exogenous sources, the creatinine output is practically independent of the protein level of the food. This is evident from table 48. The creatinine excretion is therefore considered to be an index of the magnitude of the metabolism of the tissues and especially of muscle. The daily output of creatinine is extraordinarily constant for the individual; it is not influenced by ordinary exercise or by the urine volume. The creatinine coefficient—

$$\frac{\text{milligrams creatinine excreted per day}}{\text{body weight in kilograms}}$$

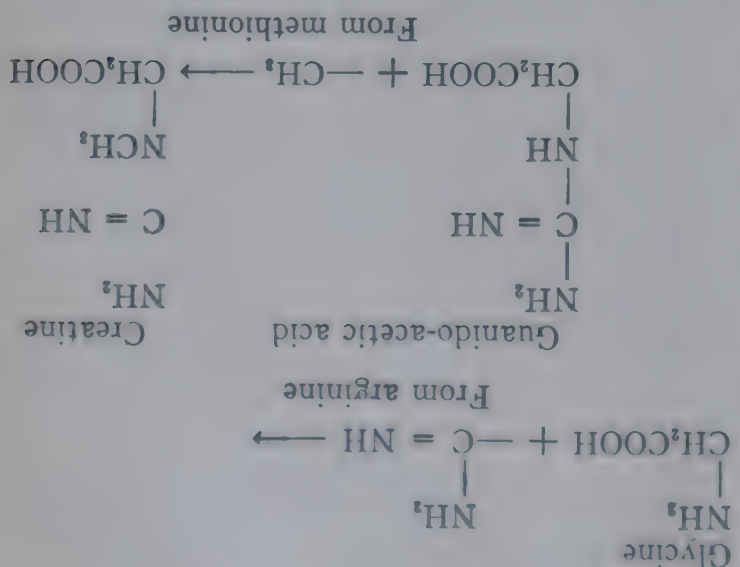
* Or creatine + creatinine, when creatinuria exists.

that glycine, which is an indispensable amino-acid for chicks, can be replaced in the diet of this species by creatine. These results pointed to arginine, guanido-acetic acid, and especially glycine as precursors of creatine.

The subject of creatine synthesis has been clarified recently through a number of experiments in which isotopes were used as markers to identify the particular substance under investigation after it had been absorbed. The administration of isotopic glycine (i.e., heavy nitrogen, N^{15} , incorporated in the glycine molecule) was shown by Bloch and Shoenheimer to give rise to creatine with a high concentration of the nitrogen isotope. Of all the other amino-acids investigated by this method, arginine alone was found to be a primary precursor of creatine. The isotope N^{15} was incorporated into the amidine part ($NH_2-C=NH$) of the arginine molecule. When the isotopic arginine was fed, the creatine isolated from the tissues of the animal was found to contain the isotope in this part of its molecule. The researches of du Vigneaud and of Borsook and Dubnoff show clearly that the methyl group of creatine is furnished by methionine. The former worker prepared methionine in which the three hydrogen atoms of the S-methyl group were present as the isotope H_3 (deuterium). When this was fed and the creatine of the animals' bodies determined, the isotope concentration indicated that nearly 70 per cent of the methyl groups of the creatine molecule had been derived from methionine. Borsook and Dubnoff incubated liver slices with guanido-acetic acid which they found was slowly converted to creatine, the conversion being hastened by the addition of methionine. Guanido-acetic acid is apparently an intermediary in the synthesis of creatine in the body; when the isotopic form of this compound is fed isotopic creatine is formed. The conclusions to be drawn from these experiments are that arginine, glycine and methionine enter into the synthesis of creatine but that other amino-acids do not serve as precursors.² The first reaction, it appears, is between the amidine part of arginine and glycine with the formation of guanido-acetic acid, arginine furnishing the amidine group of the latter. The guanido-acetic acid then under-

² The views of Beard and his associates, though not generally accepted, should be referred to here. These investigators maintain that almost any amino-acid as well as urea and other nitrogenous substances can give rise to creatine, and that creatinine is not derived from creatine but that the latter is formed by the hydration of creatinine.

goes methylation by the transference of the methyl group from methionine. Thus—



The site of creatine production is not known definitely but it is probably in the muscles. These also in all probability are the site of creatine-creatinine transformation (by dehydration). Mann and Magath found that removal of the liver was without effect upon creatinine production. The creatine which gives rise to urinary creatinine is derived very largely from the phospho-creatine of muscle.

Creatine is not, as was held by some authorities in the past, simply a waste product of protein metabolism like urea. If, for example, a large dose of creatine is fed the greater part or the whole is retained in the body.³ Creatinine, on the other hand is purely a waste product. Up to 80 per cent or more of the amount can be recovered unchanged in the urine. The investigations of recent years into the chemistry of muscular contraction have revealed the essential importance of creatine (as phosphocreatine) in the contractile process (p. 614).

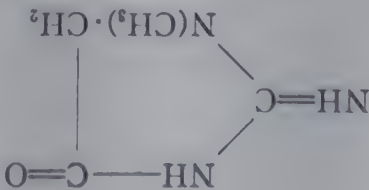
It is appropriate to mention here the results obtained with glycine in the treatment of *myasthenia gravis*. This condition, as its name implies, is a condition of profound weakness of the muscles, those of the eyes, face and throat being, as a rule, involved first. Collections of lymphocytes (lymphorrhages) and degeneration of ingested creatine is also demonstrable in man.

either sex under the following conditions; high protein diet, starvation, carbohydrate deprivation, diabetes, wasting diseases and fevers, exophthalmic goiter and in certain muscular dystrophies. The creatinuria in all of these conditions except the last is probably due to an increase in the normal catabolism of muscular tissue, the liberation of creatine occurring more rapidly than its conversion to creatinine. Protein food, for example, has a stimulating effect upon metabolism (p. 554), while in wasting diseases, fevers, etc., tissue breakdown is accelerated. Carbohydrate deprivation probably acts indirectly in that its sparing effect upon protein catabolism is absent. In the muscular dystrophies, e.g., myasthenia gravis, progressive muscular atrophy, amyotonia congenita, anterior poliomyelitis, etc., the urinary creatine is probably derived from the degenerating muscle fibers; the muscles also appear to be defective in their power to store creatine. The creatinuria of normal children has received no satisfactory explanation; it is said to be due to an increased production of creatine, induced in some way by the growth impulse, and also probably to a low capacity for creatine storage of the undeveloped muscles. Another possibility is that children have a relatively low power to convert creatine to creatinine (Hunter).

The origin of creatine and of creatinine

Creatinine is undoubtedly derived from creatine but there has been much uncertainty concerning the latter's origin. One or other of the substances to which its chemical formula suggests a relationship, e.g., guanidine, glycine, arginine, histidine, betaine or choline, has been considered as a possible precursor. The opportunity afforded by the creatinuria of muscular dystrophies has been taken advantage of by Brand and his colleagues in the investigation of this question. Various amino-acids and other guanido-compounds were fed to patients suffering from such disorders; ingested glycine, or gelatin which is rich in this amino-acid, causes a pronounced rise (40 per cent) in the creatine excretion of these patients but not of normal persons. The proportion of ingested creatine which is retained is also much less than the normal (*creatinine tolerance test*). Arginine and guanido-acetic acid (glycocycamine) were also effective. Feeding benzoic acid, which drew upon the body's glycine store for detoxication purposes (p. 391) caused a decrease in the creatine excretion. The importance of glycine in creatine synthesis is emphasized by the observation of Almqvist and Meckb

is the anhydride of creatine. Its molecular constitution is shown by the following formula



Distribution of creatine and creatinine

There are about 120 grams of creatine contained in the adult human body. Of this 98 per cent is contained in the muscles and 1.5 per cent in the nervous system. The remaining 0.5 per cent is distributed throughout the other organs of the body; of these, the testes contain it in highest concentration. The skeletal and cardiac muscles and the gravid uterus are a great deal richer in creatine than the smooth muscle of the gastrointestinal tract and elsewhere. About 80 per cent of the creatine in muscle is combined with phosphoric acid as *phosphocreatine* (p. 614). Of the striated muscles, the rapidly contracting, pale type contain more than the slowly contracting red variety (p. 824).

Creatinine is present in muscle in much smaller amounts. One hundred grams of skeletal muscle, for example, contains 200 to 300 mg. of creatine and only 10 mg. of creatinine. The creatine of whole blood amounts to from 3.5 to 5.0 mg. and the creatinine to about 2.5 mg. per 100 cc. By far the greater part, if not all, of the creatine is contained in the corpuscles. The creatinine is about equally distributed between cells and plasma.

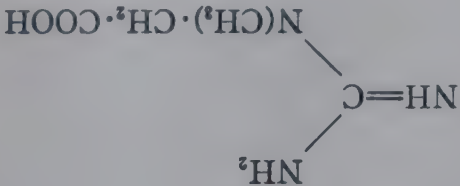
Excretion of creatine and creatinine

Creatine is normally absent from the urine of men, but is present in the urine of male and female children up to the age of puberty and frequently in the urine of women. The significance of these sex differences is not evident. In non-pregnant women the *creatinuria* is intermittent but is not related to menstruation. During pregnancy creatine is present continuously in the urine. This may be related to the high creatine content of the uterus. For two or three weeks after child-birth the quantity excreted is even higher than during pregnancy. Reduction in the muscular mass of the uterus (involution) may account in part for the high output during the puerperium, but that uterine involution is not the chief cause is shown by the fact that it occurs although Caesarian section and removal of the uterus have been performed. Creatine also appears in the urine of

tissue leads to the production of urea. Urea is very widely distributed throughout nature, being a constituent of the body fluids of the lowest forms of animal life. It is also found in plants. For this reason its formation in animals might be thought to be a function common to all tissues. But the observations of Mann and his colleagues seemed to show that in dogs urea formation is exclusively an hepatic function. After complete removal of the liver the formation of urea ceases, so that the concentration in the blood and urine falls progressively, as does also the urinary ammonia. If the kidneys as well as the liver are excised there is no accumulation of urea in the blood though the amino-acid concentration rises. Also, after the injection of glycine or alanine into the hepatectomized animal, in contrast to the result obtained in the normal animal, the concentration of the injected amino-acid rises in the blood and urine, and there is no evidence of urea production. That these results in dogs apply to man is indicated by the observation of Rabinowitch. He has reported that in a case of extensive damage to kidneys and liver (acute yellow atrophy) the excretion of urine was almost suppressed yet the blood was urea-free. The appearance of leucine and tyrosine in the urine in acute yellow atrophy of the liver may also be ascribed to the failure of deamination of these amino-acids. Nevertheless, though the liver undoubtedly plays the predominant rôle in the production of urea, certain other tissues may share to some degree in its manufacture. Graham and associates found, for example, that the active mammary gland produces not inconsiderable amounts.

CREATINE AND CREATININE

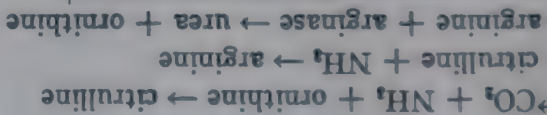
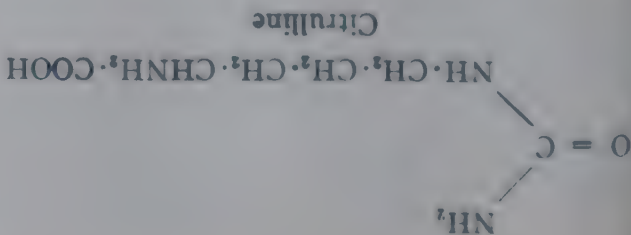
Creatine ($C_4H_9N_3O_2$) (methyl guanidine-acetic acid or methyl-glyco-cyamine) has the following structural formula



From a study of the above formula it will be seen that from a chemical viewpoint creatine may be looked upon as a derivative of glycine, of guanidine or of guanidine-acetic acid. It is also related to arginine and probably to choline. It is readily converted to creatinine.

Creatinine, $C_4H_7N_3O$ (methyl glyco-cyamidine)

(2) The addition of a second molecule of ammonia to citrulline with the production of arginine. Therefore, the production of urea from ammonia and carbonic acid may be represented thus



There is probably at least one mechanism of urea production other than that dependent upon the arginine-ornithine cycle. Leuthardt found, for example, and his findings have been confirmed by Bach, that glutamine, ammonia and carbon dioxide form urea in the absence of ornithine. Indeed, some now doubt that the importance which has been attached to the ornithin cycle in the production of urea is fully justified (see Trowell, and Gornall and Hunter).

On an ordinary mixed diet from 80 to 90 per cent of the urinary nitrogen is urea-nitrogen. The absolute amount of urea-nitrogen excreted daily is usually from 9 to 13 grams (20 to 30 grams of urea). Minimal amounts are also excreted in the sweat (p. 626), salivary, intestinal and mammary secretions. The urea-nitrogen varies with the protein content of the diet. Upon a low protein diet the output may be as low as 2 grams and on a diet rich in protein over 25 grams. The value of urea-N is therefore taken as an index of the magnitude of the catabolism of food protein (exogenous metabolism, see table, p. 550).

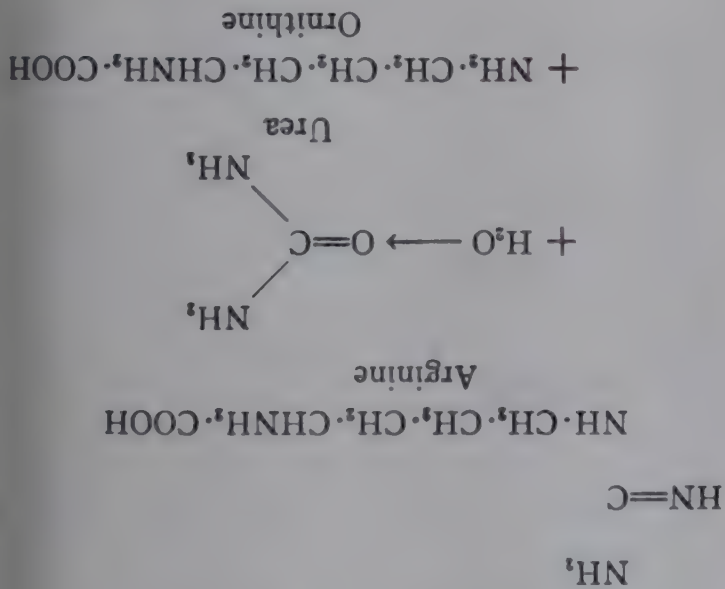
The blood contains from 8 to 15 mg. of urea-N (18 to 35 mg. urea) per 100 cc. Urea is readily diffusible and is found in about the same concentration in the various tissues and other fluids, e.g., lymph, bile, cerebrospinal fluid and pancreatic juice, as in blood. The kidney, however, is an exception since it contains some 150 to 200 mg. of urea per 100 grams of tissue. We have already seen that the urinary ammonia is formed from urea and amino-acids in the kidney (p. 391).

THE SITE OF UREA PRODUCTION. It has long been known that the liver is an important site of urea formation. Perfusion of the liver with amino-acids or their addition to sliced liver

THE END PRODUCTS OF PROTEIN

METABOLISM UREA

The great proportion of the nitrogen released by the catabolism of the amino-acids appears in the urine of man, mammals, amphibia and fish as urea. In birds and reptiles, on the other hand, the chief end product of protein breakdown is *uric acid*. In man the latter is derived from the metabolism of the purines (p. 565). Urea is formed directly (i.e., without preliminary deamination), from *arginine*, which is hydrolyzed by the action of an enzyme—*arginase*—into *urea* and *ornithine*. Arginase is present in the liver of mammals but not in that of birds. The reaction may be represented thus



It is only within recent years that the importance of this mechanism in the production of urea has been realized and its details disclosed. It has been thought to account for the greater proportion of the urea formed in the body. When ornithine was incubated with slices of liver in the presence of ammonia and carbonic acid, large amounts of urea were formed. It is supposed that the ornithine combines with the ammonia and carbonic acid to form arginine which in turn is hydrolyzed by arginase into urea and ornithine. Thus it appears that arginine serves as an intermediary in the production of urea from the ammonia supplied by the other amino-acids. The ornithine liberated by the decomposition of arginine is used over again. Ornithine thus acts after the manner of a catalyst to facilitate urea production.

According to Krebs and Henseleit, the formation of arginine from ornithine occurs in two steps. (1) The formation of a substance called *citrulline* by the addition of a molecule each of ammonia and carbon dioxide to ornithine.

It was shown by Schoenheimer and his associates, using isotopic amino-acids, that dietary nitrogen was constantly and rapidly being incorporated into plasma proteins and into the proteins of liver, kidney and intestinal tract as well as, but more slowly, into the proteins, including hemoglobin, of the red cells. Furthermore, nitrogen is continually being exchanged between the various tissues. In the new theory originally proposed by Borsook and Keighley, protein metabolism is conceived as a dynamic mechanism in which breakdown and resynthesis proceed hand and hand, dietary protein replacing tissue nitrogen and the nitrogen of different organs undergoing continuous interchange. Even in the starving animal tissue protein does not undergo catabolism alone, but is being continuously resynthesized, new protein being formed in one tissue from nitrogen derived from another.

Protein storage—labile protein

Though it is accepted beyond all question that fat and carbohydrate are stored, it was not the belief that the body accumulated reserves of protein. (The increase in body protein which occurs during growth, pregnancy or athletic training cannot be considered as protein storage in the ordinary sense.) It has been shown, however, that protein storage also occurs. During starvation or upon a non-protein diet this *deposit protein* or *labile protein* is drawn upon. When protein is fed after a period of protein deprivation, retention of nitrogen occurs as a result of the reaccumulation of the protein stores. After these have been replenished the quantity of nitrogen excreted in the urine again balances that taken in the food. There is thus a lag in the establishment of nitrogen equilibrium in changing from one protein level to another. All organs and tissues including the blood plasma apparently contain protein in this form, a form which is not an intimate constituent of tissue structure and can be quickly mobilized upon demand. The plasma proteins are also thought to constitute a reserve store of protein upon which the body can draw during a period of protein starvation. According to Boothby and associates, the myxoedematous swelling characteristic of hypothyroidism (p. 673) is due to an increase in the quantity of deposit protein. The excessive deposit is broken down under the influence of thyroxine. The latter also reduces the quantity of deposit protein in the normal subject.

acid, alanine and arginine. The perfusion experiments just mentioned suggest that alanine may be synthesized from the derivatives of carbohydrate metabolism plus the ammonia which would otherwise be excreted as urea. Other more complex amino-acids, e.g., tryptophane, histidine, etc. (p. 542) contain special groupings which cannot be formed in the body. They are therefore essential constituents of the diet (p. 559). If, however, the special groups are supplied, as in the form of the keto- or hydroxy-acid, the corresponding amino-acid can in some instances be formed.

THE CLASSICAL AS OPPOSED TO THE MODERN VIEW OF PROTEIN METABOLISM

The classical theory of protein metabolism as proposed by Folin has held the field for many years. It was based upon the urinary excretion of nitrogen. Folin was pointed out that under widely altered intakes of nitrogen the quantities of creatinine and neutral sulphur excreted in the urine remained remarkably constant, whereas the excretion of urea varied in amount. Creatinine and neutral sulphur were thought to be derived from the "wear and tear" of body tissue and were taken as an index of *endogenous* protein metabolism. Urea, on the other hand, was believed to be derived solely from the catabolism of dietary protein and was referred to as the *exogenous* quota of protein metabolism. Several facts, discovered chiefly through experiments with isotopic nitrogen (N^{15}) used as a "tracer," are not in accord with Folin's theory. The body structure is not like a machine, the composition of whose parts remains fixed and unchanged except for a certain loss from wear and tear which is repaired from dietary material, but is constantly in a state of flux. It has been shown, for example, that when amino-acids containing isotopic nitrogen are fed to an animal in nitrogen equilibrium only small quantities of isotopic nitrogen appear in the urine, whereas, a relatively large amount (about half) can be recovered from the tissues. In other words, the dietary nitrogen had replaced catabolized tissue protein whose nitrogen was excreted in the urine. The nitrogen derived from tissue protein, thus, far exceeded in amount that which the classical theory attributes simply to wear and tear. It has also been found, contrary to expectations, were creatinine and neutral sulphur excretion an index of endogenous protein catabolism, that increasing the metabolic rate or of the endogenous protein catabolism does not increase significantly the urinary excretion of these

THE SYNTHESIS OF AMINO-ACIDS

That the body tissues, given the necessary amino-acids, can link them together and so synthesize protein is, of course, unquestioned. The extent to which the amino-acids themselves can be synthesized is a more difficult question to decide. Undoubtedly the body is able to synthesize glycine—the simplest amino-acid. For example, milk proteins contain no more than 0.1 to 0.3 per cent of glycine, yet from 100 grams of the former the suckling animal can build up 78 grams tissue protein containing 2.5 grams of glycine (Magnus-Levy). Also, the liver and kidney detoxicate benzoic acid by combining it with glycine to form hippuric acid which is excreted in the urine. When large quantities of benzoic acid are fed, the glycine in the excreted hippuric acid is greater in amount than that which could have been supplied preformed from body tissue. Analogous experiments with the detoxication of phenylacetic acid indicate that glutamic acid can also be synthesized. The mode by which synthesis of the amino-acids takes place is obscure. Experiments suggest, however, that synthesis can occur from α -keto acids or hydroxy-acids and ammonia by a process of reduction. Thus

$$R \cdot CH_2CO \cdot COOH + NH_3 \rightarrow R \cdot CH_2COHNH_2 \cdot COOH \rightarrow R \cdot CH_2COHNH_2 \cdot COOH + H_2O$$

ketonic acid hydroxy-acid amino-acid

Embsen found that alanine was formed by the surviving liver perfused with blood to which the ammonium salt of pyruvic acid had been added. Phenylalanine and tyrosine were also formed when the liver was perfused with the ammonium salts of the corresponding ketonic acids. Even the addition of ammonium chloride to the fluid perfusing a glycogen-rich liver resulted in the production of alanine. The latter also followed perfusion with ammonium lactate. Furthermore, it was shown by Knoop that when γ -phenyl- α -keto-butyric acid was administered to dogs the corresponding amino-acid appeared in the urine, while the experiments of Cox and Rose and of Sherwin and their associates indicate that histidine, an essential amino-acid, can be formed in the body when imidazole pyruvic acid or imidazole lactic acid is fed. The synthesis of arginine has also been demonstrated by Rose and his colleagues.

To sum up: it is established that glycine can be synthesized from precursors already present in the body. The same may also be said for glutamic

peptides) of the injected protein are utilized by the tissue cells.

THE FATE OF AMINO-ACIDS AFTER ABSORPTION

DEAMINATION. Those amino-acids which are not required intact for building body protein, for the manufacture of hormones or other secretions, are broken up. The incombustible amino group (NH_2) is split from the amino-acid molecule and the ammonia so produced is combined with carbon dioxide to form urea (p. 546). This is excreted in the urine. The fatty acid residue may either undergo oxidation, and thus furnish energy to the body, or be transformed into glucose. The glucose may be burned or be stored as glycogen, or again it may be transformed into fat. Not all amino-acids, however, are sugar or glycogen formers. Those which play this rôle are *glycine, alanine, aspartic, glutamic and hydroxyglutamic acids, serine, cystine, arginine and proline*. With the exception of arginine and proline these are all straight chain amino-acids with less than six carbon atoms. The quantity of these amino-acids present in 100 grams of protein is sufficient to form some 58 grams of glucose.¹ A depancreatized or phloridzinized dog, for instance, or the subject of severe diabetes, though upon a carbohydrate-

¹ Since different proteins contain varying amounts of sugar-forming amino-acids, this is an average figure. It was arrived at by calculation from the proportion of glucose (dextrose) to nitrogen in the urine—the so-called G:N (or D:N) ratio—in phloridzinized dogs fed exclusively upon protein or during a period of starvation. Lusk found the G:N ratio under such circumstances to be 3.65:1. The nitrogen of the urine is derived, of course, practically entirely from protein. The urinary glucose of an animal under the influence of phloridzin and whose glycogen stores have been exhausted is also assumed to be derived exclusively from protein. Now each gram of urinary nitrogen represents catabolism of 6.25 grams of protein. Therefore with a G:N ratio of 3.65:1 every 3.65 grams of glucose secreted indicates the conversion of 6.25 grams of protein. So

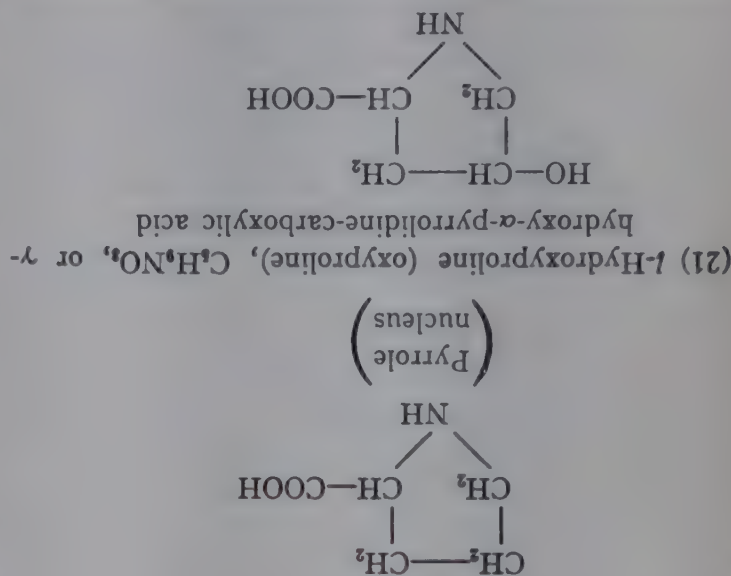
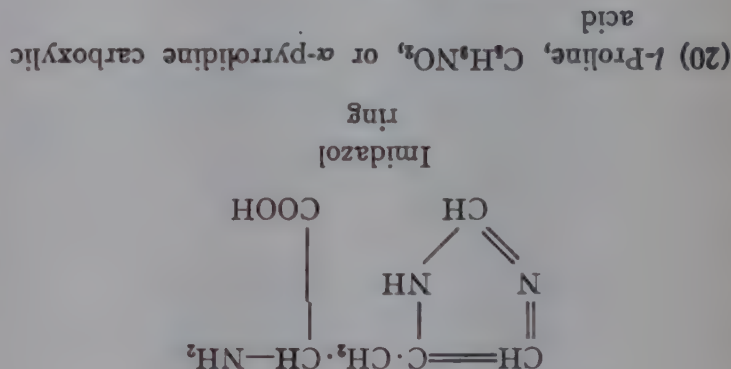
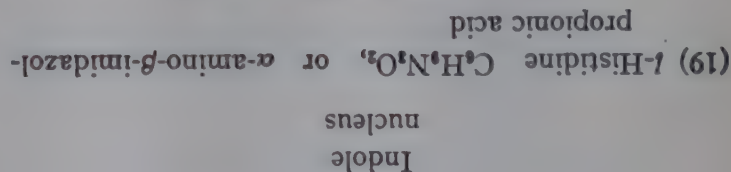
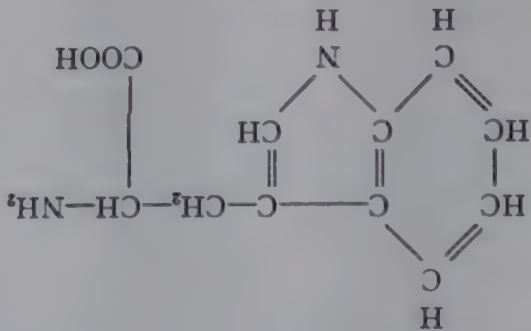
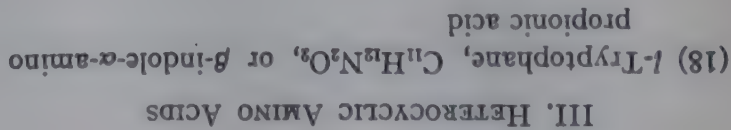
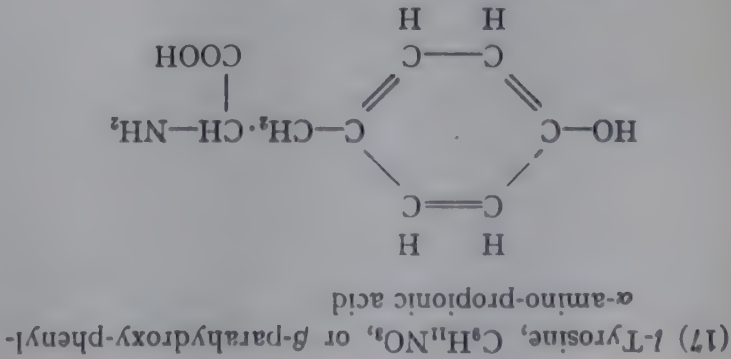
$$\frac{3.65}{6.25} \times 100 = 58 \text{ per cent}$$

In diabetic (depancreatized) animals during starvation or upon a protein diet the G:N ratios obtained by different observers vary widely. Minkowski's figure of 2.8:1 is most usually quoted (this would indicate the conversion of 45 per cent of protein to sugar). Macleod and his associates, however, have obtained ratios in depancreatized dogs after the withdrawal of insulin as high as 6:1 in some experiments, and less than 2:1 in others. The ratio did not show a constant value, either in different animals or in the same animal at different times. They therefore seriously question the reliability of the G:N ratio as an index of the extent of the protein to glucose conversion, and consider that protein is not the only source of the urinary glucose.

proteins contained in these substances, result in cutaneous eruptions and sometimes localized edema. Minute amounts of the protein apparently enter the blood stream in an unchanged or partially digested state. Asthma, hay fever and other allergic conditions (see also p. 366) have been traced to foreign proteins (pollen, cat or horse hair, feathers, etc.) entering the body through the respiratory passages.

Most proteins introduced directly into the blood stream or absorbed unchanged from the intestinal tract are utilized to a very limited extent or not at all, and may be toxic. The same may be said for proteoses and peptones. Homologous plasma protein is a notable exception. Whipple and his associates found that dogs could be maintained in nitrogenous equilibrium by the intravenous injection of plasma from other dogs as the sole source of protein. A suitable assortment of amino-acids, such as an hydrolysate of casein supplemented by cystine and tryptophane, injected intravenously, is capable of maintaining an animal in nitrogenous equilibrium. It is possible that a solution of gelatin or of isinglass suitably supplemented with the missing amino acids might be used.

It is the general belief that the tissues are unable to utilize protein degradation products larger than single amino-acids, but must receive their building materials already separated into single "stones" or "bricks", for the amino-acid assortment in the ingested or injected protein will ordinarily not be identical with those composing the tissues of the animal, and therefore cannot be built as a group into its body protein. On the other hand, the reduction of all food protein to its amino-acid constituents enables the cells to choose assortments peculiar to their own structure. Generally speaking, this conception is probably true, but the experiments of Howland and Hawkins suggest the possibility that it is not invariably under all conditions. They found that homologous plasma protein injected intravenously into dogs disappeared from the blood stream within 24 hours, yet there was no detectable rise in the amino-acid concentration of the blood, nor was any increase of urinary nitrogen observed. In phloridzinized animals the injections caused no rise in the excretion of sugar. The oral administration of plasma protein, on the contrary, resulted in an increased urinary excretion of both nitrogen and sugar in phloridzinized animals. These observations suggest in explanation of their results that large aggregates of amino-acids (poly-



Thyroxine (p. 682), *3-5-diiodotyrosine* or *iodogorgoic ornithine* (p. 546) would have to be added in order to complete the list of known amino-acids.

THE ABSORPTION OF PROTEIN

isoelectric point—*isoelectric precipitation*.

According, however, to the *Zwiler hypothesis* the ampholyte molecule gives off, at the isoelectric point, *equal numbers* of basic and acid ions, thus leaving ions—the so-called *Zwitterions* (Ger. *Zwitter* = herma-phrodite)—holding equal numbers of negative and positive charges (formula II). Many proteins, e.g., metaproteins, casein, etc. are almost insoluble at the isoelectric point.

Under ordinary circumstances only negligible amounts of unchanged protein, or even such of its derivatives as proteoses, peptones and polypeptides, are absorbed into the blood from the alimentary tract. Generally speaking the protein molecule must first be hydrolyzed into its constituent amino acids. These are absorbed from the small intestine but not from the stomach. They enter the portal blood and, though to a very much less extent, into the lymph (chyle) and thence into thoracic duct.

Small amounts of certain proteins, e.g., raw egg white and blood serum are sometimes absorbed from the intestine into the blood stream. They are excreted in the urine to a large extent unchanged. Such absorption, which occurs more readily in young animals and children, should be regarded as a defect rather than as representing a physiological process. Nevertheless, experiments have shown that small quantities of protein introduced parenterally may be utilized by the tissues, and may even be capable of maintaining nitrogen equilibrium (p. 551). Though it is possible that the injected protein was broken down into its constituent amino-acids by the general tissue cells, it is more probable that this function was performed by the cells of the intestinal wall, and that the latter are necessary for the digestion even of protein introduced parenterally. It is, however, only for a short period and to a very limited extent that the body can utilize injected protein, for after a number of injections immunity is established to the foreign protein; an antibody known as a *precipitin* is formed which causes precipitation of the protein. Furthermore, if a subsequent injection is given two weeks or so after a single injection or after the last of a series of such injections, a most serious toxic state—*anaphylaxis*—may develop and prove fatal. In the human subject such anaphylactic (or anaphylactoid) reactions may follow the second injection of a foreign protein, e.g., diphtheria antitoxin (horse serum) or antitetanic serum. Skin rashes such as urticaria, erythema, eczema, giant edema, etc., or pain and swelling of the joints may occur. Collapse and death occasionally result (p. 263). The sensitivity of some persons to certain proteins is also sometimes responsible for dietary idiosyncrasies. Certain foods such as shell-fish, milk, strawberries, celery, etc., when ingested by persons sensitive to the

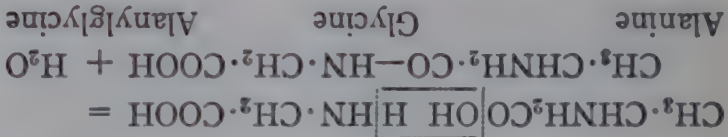
Classification of the amino-acids	
I. ALIPHATIC AMINO-ACIDS	
A. Monamino-monocarboxylic acids	
1) Glycine (or glycocoll) $C_2H_5NO_2$, or amino-acetic acid	$\begin{array}{c} \text{COOH} \\ \\ \text{CH}_2-\text{NH}_2 \end{array}$
2) <i>D</i> -Alanine $C_3H_7NO_2$ or α -amino-propionic acid	$\begin{array}{c} \text{COOH} \\ \\ \text{CH}_3-\text{CH}-\text{NH}_2 \end{array}$
3) <i>L</i> -Serine, $C_3H_7NO_2$, or β -hydroxy- α -amino-propionic acid	$\begin{array}{c} \text{OH} \quad \text{COOH} \\ \quad \\ \text{CH}_2-\text{CH}-\text{NH}_2 \end{array}$
4) <i>D</i> -Threonine $C_4H_9NO_2$, β -hydroxy- α -aminobutyric acid	$\begin{array}{c} \text{OH} \quad \text{COOH} \\ \quad \\ \text{CH}_2-\text{CH}-\text{CH}-\text{NH}_2 \\ \\ \text{COOH} \end{array}$
5) <i>D</i> -Valine $C_5H_{11}NO_2$ or α -amino-isovaleric acid	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}-\text{CH}-\text{NH}_2 \\ \\ \text{COOH} \end{array}$
6) Norleucine $C_6H_{13}NO_2$ α -amino-caproic acid	$\begin{array}{c} \text{CH}_3 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}-\text{NH}_2 \\ \\ \text{COOH} \end{array}$
7) <i>L</i> -Leucine, $C_6H_{13}NO_2$, α -amino-isocaproic acid	$\begin{array}{c} \text{CH}_3 \quad \text{CH}_3 \cdot \text{CH}_2 \\ \diagdown \quad \diagup \\ \text{CH}-\text{CH}_2 \cdot \text{CH}-\text{NH}_2 \\ \\ \text{COOH} \end{array}$
8) <i>D</i> -Isoleucine, $C_6H_{13}NO_2$, or β -methyl- β -ethyl- α -amino-propionic acid	$\begin{array}{c} \text{CH}_3 \cdot \text{CH}_2 \quad \text{COOH} \\ \diagdown \quad \\ \text{CH}-\text{CH}-\text{NH}_2 \\ \\ \text{CH}_3 \end{array}$
II. AROMATIC AMINO-ACIDS	
(16) <i>L</i> -Phenylalanine, $C_9H_{11}NO_2$, or β -phenyl- α -amino-propionic acid	$\begin{array}{c} \text{H} \quad \text{H} \\ \quad \\ \text{C}-\text{C} \\ // \quad \backslash \\ \text{C}-\text{CH}_2 \cdot \text{CH}-\text{NH}_2 \\ \\ \text{COOH} \end{array}$
B. Monamino-dicarboxylic acids	
(9) <i>L</i> -Aspartic acid, $C_4H_7NO_4$, or amino-succinic acid	$\begin{array}{c} \text{COOH} \\ \\ \text{COOH} \cdot \text{CH}_2 \cdot \text{CH}-\text{NH}_2 \end{array}$
(10) <i>D</i> -Glutamic acid, $C_5H_9NO_4$, or α -amino-glutaric acid	$\begin{array}{c} \text{COOH} \\ \\ \text{COOH} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}-\text{NH}_2 \end{array}$
(11) <i>D</i> -Hydroxyglutamic acid, $C_5H_9NO_5$, or α -amino- β -hydroxy-glutaric acid	$\begin{array}{c} \text{COOH} \cdot \text{CH}_2 \cdot \text{CHOH} \cdot \text{CH}-\text{NH}_2 \\ \\ \text{COOH} \end{array}$
C. Diamino-monocarboxylic acids	
(12) <i>D</i> -Arginine, $C_6H_{14}N_4O_2$, or δ -guanidin- α -amino-valeric acid	$\begin{array}{c} \text{NH}_2 \\ \\ \text{HN}=\text{C}-\text{NH} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}-\text{NH}_2 \\ \\ \text{COOH} \end{array}$
(13) <i>D</i> -Lysine, $C_6H_{14}N_2O_2$, or α - ϵ -diamino-caproic acid	$\begin{array}{c} \text{NH}_2 \\ \\ \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}-\text{NH}_2 \\ \\ \text{COOH} \end{array}$
D. Sulphur containing amino-acids	
(14) <i>L</i> -Cystine, $C_6H_{12}N_2S_2O_4$, (or di-cysteine) or di- $(\beta$ -thio- α -amino-propionic acid)	$\begin{array}{c} \text{CH}_3-\text{S}-\text{S}-\text{CH}_3 \\ \quad \\ \text{CH}-\text{NH}_2 \quad \text{CH}-\text{NH}_2 \\ \quad \\ \text{COOH} \quad \text{COOH} \end{array}$
(15) <i>L</i> -Methionine, $C_5H_{11}SNO_2$, or α -amino- γ -methyl-thiol-n-butyric acid	$\begin{array}{c} \text{CH}_3 \cdot \text{S} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}-\text{NH}_2 \\ \\ \text{COOH} \end{array}$

TABLE 47

TABLE 46—Continued

CLASS OF PROTEIN	CHARACTERISTICS	EXAMPLES
C. Derivatives of proteins—derived proteins.—Continued		
(2) Metaproteins	Formed in a later stage of the action of acid or alkali	Acid metaprotein, alkali metaprotein
(3) Coagulated proteins	Formed by the action of heat or of alcohol upon solutions of proteins	Albumose from albumen, globulose from globulin, caseose from casein
(b) Secondary derivatives	Formed by the action of pepsin or trypsin upon proteins. They are soluble in water from which they are precipitated by saturation with ammonium sulphate. They are incoagulable by heat	
(c) Peptones	These represent a further stage in action of proteolytic enzymes. They are soluble in water but are not precipitated from an aqueous solution by ammonium sulphate. They are not coagulated by heat	
(d) Peptides, di-peptides, tripeptides and polypeptides	Products formed in the final stages of proteolytic digestion	Glycyl-alanine, leucyl-glutamic acid, etc.

amino-acid with the acid group of another and the liberation of a molecule of water. Thus



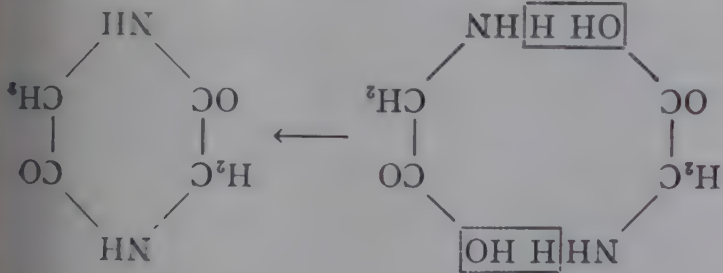
The junction, CO-NH, whereby amino-acids become grouped together is called the *peptide linkage*. The reverse process, namely, the separation of amino-acids from one another is also effected at this link in the chain, a molecule of water first being taken up. This process, which is called *hydrolysis*, may be illustrated thus.



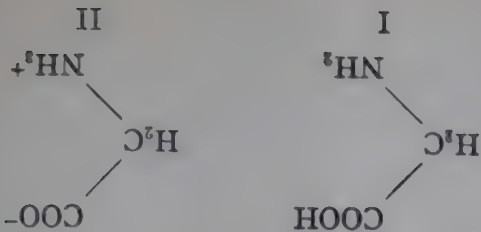
Alanylglycine alanine glycine

Besides the simple chain-like combination of the amino-acids in the protein molecule a smaller proportion are believed to be united to form a series of closed-ring compounds—*diketopiperazines*. The ring structure is produced through the junction of free amino and carboxyl groups of amino-acids. Below is shown the production of diketopiperazine by the condensation of two molecules of glycine.

Protein, as a consequence of its constitution of amino-acids linked together as described above, con-



tains free NH₂ and COOH groups. By virtue of these it can act either as a weak acid or as a weak base; in acid solution it acts as a base yielding cations to form protein chloride, sulphate, etc. In alkaline solution it acts as an acid, yielding anions to form proteinates of sodium, potassium, etc. Substances which behave in this manner are termed *amphoteric*. Proteins are therefore amphoteric electrolytes or *ampholytes*. The extent to which a protein dissociates, i.e., yields anions or cations, depends upon the hydrogen ion concentration. At a certain critical hydrogen ion concentration which varies with different proteins, the protein molecule is electrically neutral. This is called the *isoelectric point*. The neutrality of the molecule at the critical hydrogen ion concentration has been supposed to be due to its dissociation being at a minimum, that is, to its giving off minimal numbers of either basic (+) or acid (−) ions (formula I below).



A. Simple proteins		B. Compound proteins	
<p>Albumins—Soluble in water and coagulable by heat. Present in both animal and plant sources.</p> <p>Globulins—Soluble in water and coagulable by heat. Found in both animal and plant sources.</p> <p>Proteins in plants—Insoluble in water. Found only in plants. Insoluble in water, soluble in alcohol, but soluble in very dilute alkali.</p> <p>Found in plants—Insoluble in water, soluble in alkali, but soluble in very dilute alkali.</p> <p>Found in animals—Insoluble in water, soluble in alkali, but soluble in very dilute alkali.</p> <p>Found in both animal and plant sources—Insoluble in water, soluble in alkali, but soluble in very dilute alkali.</p>	<p>Found in both animal and plant sources—Insoluble in water, soluble in alkali, but soluble in very dilute alkali.</p> <p>Found in animals—Insoluble in water, soluble in alkali, but soluble in very dilute alkali.</p> <p>Found in plants—Insoluble in water, soluble in alkali, but soluble in very dilute alkali.</p> <p>Found in both animal and plant sources—Insoluble in water, soluble in alkali, but soluble in very dilute alkali.</p>	<p>Found in both animal and plant sources—Insoluble in water, soluble in alkali, but soluble in very dilute alkali.</p> <p>Found in animals—Insoluble in water, soluble in alkali, but soluble in very dilute alkali.</p> <p>Found in plants—Insoluble in water, soluble in alkali, but soluble in very dilute alkali.</p> <p>Found in both animal and plant sources—Insoluble in water, soluble in alkali, but soluble in very dilute alkali.</p>	<p>Found in both animal and plant sources—Insoluble in water, soluble in alkali, but soluble in very dilute alkali.</p> <p>Found in animals—Insoluble in water, soluble in alkali, but soluble in very dilute alkali.</p> <p>Found in plants—Insoluble in water, soluble in alkali, but soluble in very dilute alkali.</p> <p>Found in both animal and plant sources—Insoluble in water, soluble in alkali, but soluble in very dilute alkali.</p>

GENERAL DESCRIPTION AND CLASSIFICATION OF

PROTEINS

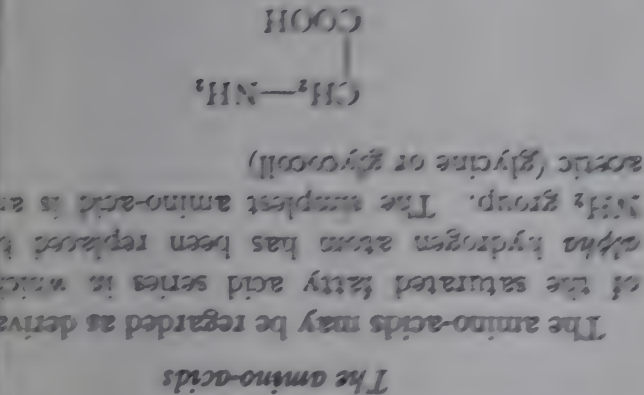
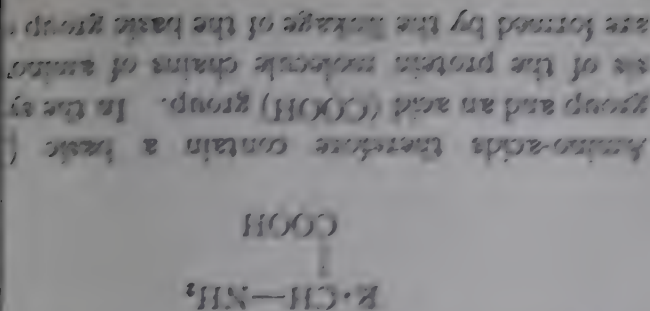
Protein is a basic constituent of protoplasm and consequently forms a proportion of all living tissues—animal or vegetable; of some tissues, e.g., muscle, it is the predominant solid constituent. It differs from the other foodstuffs—carbohydrates and fats—in containing (in addition to carbon, hydrogen and oxygen) nitrogen, sulphur and usually phosphorus. The molecules of certain proteins contain a prosthetic group, e.g., haemoglobin, glycogenase, leucine aminase, nucleoproteins, etc.

A classification and brief description of the various types of protein are given in table 46.

THE PROTEIN MOLECULE

The protein molecule is constructed of a number of units linked together. These units or "building stones" are called amino-acids. Some 23 different amino-acids have been identified as constituents of the protein molecule (see table 47). Some proteins contain nearly all of these in varying proportions; in others such as gelatin there are only 14 or 15 different kinds, some essential amino-acids being missing, while such simple proteins as the protamines, euryne and salmine, contain only 3 and 4, respectively. The single amino-acids have molecular weights ranging from 75 for glycine to over 200 for tyrosine and nearly 800 for threonine. The molecular weights of those proteins composed of large aggregations of amino-acids are correspondingly great and extend over a very wide range. The molecular weight of egg albumin, for example, is 35,000, that of haemocyanin, 5,000,000.

Protein molecules also vary in shape. Studies of protein structure by means of X-ray diffraction photography, reveal that the molecules of some proteins, such as keratin, collagen and myosin—the so-called fibrous proteins—have an elongated fibre-like form, resulting, it is believed, from the extended arrangement of the polypeptide layers of which the molecule is constructed (see below). When reversed with molecules assume elongated and further on return to their previous lengths when released from the stretching force. The



changes in length are described as being folding and unfolding of the polypeptide chain in a concertina-like fashion. Other proteins are folded or arranged into a lattice pattern form a compact structure of a more or less globular shape. Unfolding and the assumption of a permanent extended form is associated with denaturation. Proteins of approximately the same molecular weight may differ considerably in molecular structure and for this reason may differ in such physical properties as elasticity, osmotic pressure or viscosity. The fundamental structure of all proteins is believed by Astbury to be fibrous, but the intermolecular arrangement of the polypeptide chains varies widely between different types and in the same protein under different conditions. Thus a variety of patterns produced.

The average elementary composition of a molecule of a protein such as albumin or globulin is as follows: C, 54 per cent; H, 7 per cent; N, 16 per cent; S, 1 per cent; O, 22 per cent.

The amino-acids

The amino-acids may be regarded as derivatives of the saturated fatty acid series in which the α hydrogen atom has been replaced by an NH_2 group. The simplest amino-acid is aspartic (glycine or glycocoll):

that the metabolism of the new-born infant and the post-partum metabolism of the mother added together practically equalled the metabolism of the pregnant state near the end of term. Boothby and Sandiford estimated the surface area of the fetus throughout gestation and concluded that the excess heat production of the pregnant state was derived from the fetus and the increased mass of the maternal structures, the energy

TABLE 43
(Relation of height and weight to surface area after Du Bois)

WEIGHT IN KILOGRAMS		HEIGHT IN CENTIMETERS																			
		25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105			
200	1.91	1.97	2.03	2.09	2.15	2.21	2.26	2.31	2.36	2.41	2.47	2.52	2.57	2.62	2.67	2.72	2.77	2.82			
195	1.87	1.93	1.99	2.05	2.11	2.17	2.22	2.27	2.32	2.37	2.42	2.47	2.52	2.57	2.62	2.67	2.72	2.77			
190	1.84	1.90	1.96	2.02	2.08	2.13	2.18	2.23	2.28	2.33	2.38	2.43	2.48	2.53	2.58	2.63	2.68	2.73			
185	1.80	1.86	1.92	1.98	2.04	2.09	2.14	2.19	2.24	2.29	2.34	2.39	2.44	2.49	2.54	2.59	2.64	2.69			
180	1.77	1.83	1.89	1.95	2.00	2.05	2.10	2.15	2.20	2.25	2.30	2.35	2.40	2.45	2.50	2.55	2.60	2.65			
175	1.67	1.73	1.79	1.85	1.91	1.96	2.01	2.06	2.11	2.16	2.21	2.26	2.31	2.36	2.41	2.46	2.51	2.56			
170	1.63	1.69	1.75	1.81	1.86	1.91	1.96	2.01	2.06	2.11	2.16	2.21	2.26	2.31	2.36	2.41	2.46	2.51			
165	1.60	1.66	1.72	1.78	1.83	1.88	1.93	1.98	2.03	2.08	2.13	2.18	2.23	2.28	2.33	2.38	2.43	2.48			
160	1.56	1.62	1.68	1.73	1.78	1.83	1.88	1.93	1.98	2.03	2.08	2.13	2.18	2.23	2.28	2.33	2.38	2.43			
155	1.52	1.58	1.64	1.69	1.74	1.79	1.84	1.89	1.94	1.99	2.04	2.09	2.14	2.19	2.24	2.29	2.34	2.39			
150	1.48	1.54	1.60	1.65	1.70	1.75	1.80	1.85	1.90	1.95	2.00	2.05	2.10	2.15	2.20	2.25	2.30	2.35			
145	1.45	1.51	1.56	1.61	1.66	1.71	1.76	1.81	1.86	1.91	1.96	2.01	2.06	2.11	2.16	2.21	2.26	2.31			
140	1.42	1.47	1.52	1.57	1.62	1.67	1.72	1.77	1.82	1.87	1.92	1.97	2.02	2.07	2.12	2.17	2.22	2.27			
135	1.38	1.43	1.48	1.53	1.58	1.63	1.68	1.73	1.78	1.83	1.88	1.93	1.98	2.03	2.08	2.13	2.18	2.23			
130	1.35	1.40	1.45	1.50	1.55	1.60	1.65	1.70	1.75	1.80	1.85	1.90	1.95	2.00	2.05	2.10	2.15	2.20			
125	1.31	1.36	1.41	1.46	1.51	1.56	1.61	1.66	1.71	1.76	1.81	1.86	1.91	1.96	2.01	2.06	2.11	2.16			
120	1.27	1.31	1.35	1.40	1.44	1.48	1.52	1.56	1.60	1.64	1.68	1.72	1.76	1.80	1.84	1.88	1.92	1.96			

(2) RACE AND CLIMATE. Some oriental races show a slightly lower rate (from 10 to 15 per cent)

The metabolism of the new-born is much lower than that of infants a few weeks older. Premature infants have a lower rate than those born at full term. Females have a metabolic rate a little lower than that of males in the same age group. The relationship of heat production to age and sex is given in table 44.

Man occidentals living under the same climatic conditions; others show little difference. In one oriental race (the Miao of West China) and in the Maya of Central America and the Mapuches of Chile the basal metabolic rate is actually higher than that of whites. The rate is also higher in Eskimos. The basal metabolism of white persons in a tropical climate is usually reduced. (3) HABITS. Owing to the greater development of their muscular tissues and athletes and laborers have in general a higher B.M.R. than persons leading a sedentary life. (4) PREGNANCY. The basal metabolic rate of the pregnant woman shows little change until the sixth or seventh month when the fetus causes an appreciable increase in the weight of the mother. The metabolism of the mother from this time to term is the sum of her own metabolism in the non-pregnant state and that of the fetus. It is found by Murlin and Carpenter, for example,

TABLE 44
Basal heat production per square meter of body surface
(Aub-DuBois)

AGE		MALES		FEMALES	
years		Calories per hour	Calories per day	Calories per hour	Calories per day
		per hour	per day	per hour	per day
10-12	51.5	1,236	50	46.5	1,116
12-14	50	1,200	43	1,032	960
14-16	46	1,104	40	960	912
16-18	43	1,032	38	888	876
18-20	41	984	37	876	840
20-30	39.5	948	36.5	864	816
30-40	39.5	948	36	840	816
40-50	38.5	924	35	840	816
50-60	37.5	900	34	816	816
60-70	36.5	876			

production per unit of mass of the maternal organism remaining constant. Normal preg-

The latter are derived from the break-down of nuclear material as well as from free mononucleotides, e.g., adenylic, inosinic and guanylic acids, found in muscle and glandular structures. Muscle and more especially glandular tissues, e.g., thymus, liver, kidney, pancreas, testes, etc., and leguminous vegetables are food rich in purines.

Uric acid is formed from urea in the liver of the bird, but the site of its formation in the mammal is unknown. We have already seen that in the dog uric acid accumulates in the blood after removal of the liver. On the other hand, in man, the liver is the only tissue, according to Jones, which contains xanthine oxidase, which suggests the possibility that uric acid production in the human subject is essentially a hepatic function. The results of the investigations of Folin and associates indicate that from 30 to 70 per cent of the uric acid produced by the human subject is destroyed, the remainder appearing in the urine. The liver is probably the site of uric acid destruction. Little information is available concerning the process, and its end products are unknown; allantoin is not one of them however, since human urine contains insignificant amounts of this substance, and what little is present is simply that taken preformed in the food. Uric acid is excreted in the urine as the urates of sodium, potassium and ammonium, and in the free state. After urine has been voided a crystalline deposit of urates and free uric acid appears. The average daily output of uric acid is from 0.5 to 1 gram. Of this the endogenous uric acid amounts to from 0.3 to 0.4 gram. Muscular tissue most probably furnishes the precursors of endogenous uric acid, exercise causing a rise in the uric acid of the blood, and increased excretion in the urine.

Protein (purine-free, e.g., milk, eggs) and carbohydrate foods accelerate the excretion of uric acid, and lower its level in the blood.⁵ Food fat has the reverse effect—reduced excretion and a raised level in the blood.

Small quantities (15–45 mg. daily) of purines are excreted in the urine. These include adenine (but not guanine), hypoxanthine and xanthine, as well as the methyl purines contained in beverages. The latter are caffeine (1-3-7 tri-methyl-xanthine) of coffee, *theophylline* (1-3-di-methyl-xanthine) of tea and *theobromine* (3-7 di-methyl-xanthine) of cocoa. The methyl purines

⁵ The possibility has been suggested in the past that a proportion of the uric acid formed in the human body is derived, as the great part of it is in birds, from the catabolism of protein. There is no reason to believe, however, that a conversion of this nature occurs to any significant extent.

undergo partial demethylation in the body and are excreted as mono- and di-methyl purines. It appears that theobromine is excreted entirely in this form and is not converted to uric acid. Caffeine and theophylline on the other hand are converted in considerable amounts to uric acid and excreted as such. This is an important point to bear in mind when considering dietary restrictions for gouty subjects.

GOUT

Normal blood contains, on the average, about 3 mg. (2.5 to 5.0 mg.) of uric acid per 100 cc. In gout the concentration of uric acid in blood is raised and may be as high as 10 mg. per cent while its excretion in the urine is reduced. The excretion of uric acid after a meal rich in nucleoprotein, as well as the endogenous uric acid excretion, that is, the excretion on a protein-free diet, are much less in the gouty than in the normal subject. The diminished excretion of uric acid is particularly well marked just prior to an acute attack of gout. There may be no rise, however, in the blood uric acid at this time. A characteristic feature of gout is the formation of deposits of the sodium salt of uric acid (sodium urate) in the form of crystals in the cartilaginous tissues. The deposits or *tophi*, as they are called, occur most commonly about the joints of the great toes and fingers. During the gouty attack the joint becomes acutely inflamed and tender. The etiology of gout is obscure. One type of the disease occurs in association with chronic lead poisoning.

There is no reason to believe that the *hyperuricemia* of gout is the result of an increased production of uric acid in the body, nor is it due, apparently, to diminished destruction of uric acid. It is quite evidently due to reduced excretion. Nevertheless, the uric acid retention is not due to renal failure in the ordinary sense of the term, and though gout and kidney disease are not infrequently associated, the high concentration of uric acid in the blood of the gouty subjects is the forerunner of the kidney damage, rather than that the latter is the primary cause of uric acid retention. Furthermore, a level of uric acid may be present as in nephritis and other conditions without any sign of gout. These facts make it difficult to find a satisfactory explanation for the high uric acid level in the blood in gout. Minkowski suggested that normally uric acid existed in blood in combination with a nucleoside which was decomposed by the kidney cells, the uric acid being excreted. In gout, it was supposed, this specific renal function was impaired. Benedict and his colleagues have obtained evidence in favor of such a view. They claim to have demonstrated the presence of two forms of uric acid in the blood of the ox and other animals, and in man. Freshly drawn ox blood contains 0.5 mg. per cent of uric

acid. Ten times this amount was obtained when the blood had been allowed to stand, or had been boiled with hydrochloric acid. This suggested that the uric acid was present largely in some stable, combined form which was decomposed by the action of an enzyme or by treatment with acid. The combined form is present exclusively in the erythrocytes. It is made up of a molecule each of uric acid and a pentose—d-ribose.

The formation of tophi is not simply the result of the saturation of the blood with uric acid. The concentration of uric acid never reaches the limit of its solubility in blood. In other conditions, e.g., nephritis and leukemia, associated with a high blood uric acid, deposits do not occur: some local factor apparently is necessary for deposition to occur. The process is possibly in the nature of vicarious excretion of uric acid into certain tissues (Benedict) wherein, the uric acid upon reaching the saturation point, is deposited as crystals of sodium urate.

The treatment of gout is directed toward the reduction of the purine intake. We have seen that carbohydrates and purine-free proteins increase uric acid excretion at the same time lowering the blood level, and that fats have the opposite effect. The diet should be planned with these facts in mind. Salicylates, aspirin, cinchophen (atophan) which are used in the treatment of gout

have been shown to increase uric acid excretion and to lower the level of blood uric acid. Alcohol appears to exert little effect upon the latter though it is usually banned from the diet. Coffee and tea since their methyl purines are partly excreted as uric acid are restricted.

Other conditions associated with a high level blood uric acid are:

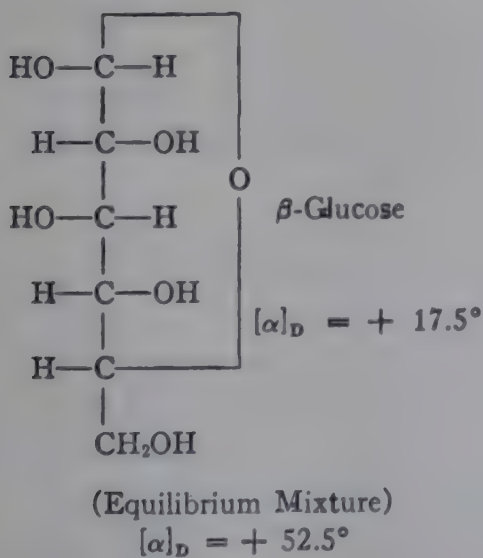
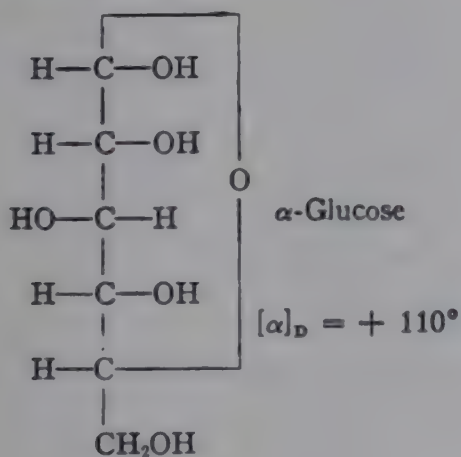
(a) *Leukemia and polycythemia.* The elevation of the blood uric acid in these conditions is usually associated with symptoms of gout. The high level of blood uric acid is evidently due to increased production and not to failure in excretion. In leukemia, for example, the amount passed daily in the urine may be as much as 12 grams. The increased uric acid production in this condition is probably due to the disintegration of body tissue, generally rather than, as has been supposed, to the destruction of white cells. (b) *Pneumonia.* (c) *Nephritis.* In renal failure the uric acid is one of the first of the nitrogenous substances of the blood to show a rise. (d) *Lead poisoning.* (e) *Toxemias of pregnancy.* (f) In certain other conditions associated with a high non-protein nitrogen of the blood.

CHAPTER L

CARBOHYDRATE METABOLISM

Since all carbohydrates are soluble in water these constituents accumulate in the extract when a tissue is thoroughly extracted with this solvent. Hot water is more effective than cold in extraction and has the further advantage that enzymic actions are inhibited. Thus the carbohydrate substances in the extract are more nearly in the form in which they occur in the living tissues.

Without doubt the carbohydrate substance most important in metabolism is glucose. All organisms appear to be able to utilize glucose. Glucose, sometimes called dextrose because its solution rotates the plane of polarized light in a dextro-rotatory direction and often written d-glucose, dissolves in water to give an equilibrium mixture of α and β -glucose, approximately two-thirds of the glucose being of the α form. The formulae of these two isomers are written.



It will be noted that a cyclic structure has been accorded the glucose molecule.¹ In this case the ring is composed of five carbon atoms and one

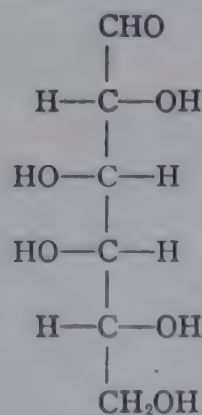
¹To account for the characteristic reducing properties of glucose it is presumed that in solution there

exists a very small amount of the open chain aldehydic form in equilibrium with the cyclic forms.

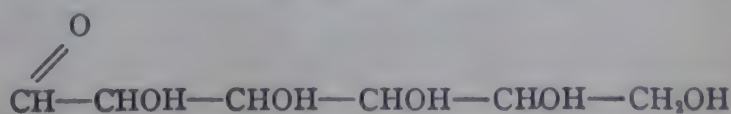
oxygen atom, sometimes referred to as an amylenic oxidic ring. α and β isomers of glucose may also possess a ring composed of four carbon atoms and one oxygen atom. This is the so-called γ -glucose. Such a ring is a butylene oxidic ring. These forms of glucose are very reactive, that is, unstable. They have not been isolated. It may be pointed out, as an example of their reactivity, that they reduce Fehling's solution in the cold. Because of this marked reactivity it has been postulated that such compounds must be the first intermediaries in glucose metabolism. But there is no conclusive evidence for such a change, and all theories of glucose metabolism involving the formation of a "reactive" form of glucose have very little factual basis. Glycogen, or animal starch, is a polysaccharide composed of glucose units and so is written $(\text{C}_6\text{H}_{10}\text{O}_5)_x$ [according to Haworth, $x = 12$. In liver glycogen formed from galactose x may equal 18 (Bell)]. Glycogen is widely distributed in the animal body, but the bulk occurs in the muscles and the liver. Glycogen may be isolated from tissue by hot water extraction, or more readily and completely by hot alkali. It is worthy of note that whereas polysaccharides are very stable in alkaline solution, monosaccharides (glucose, fructose, galactose, etc.) are unstable. The reverse behavior is exhibited in acid solution.

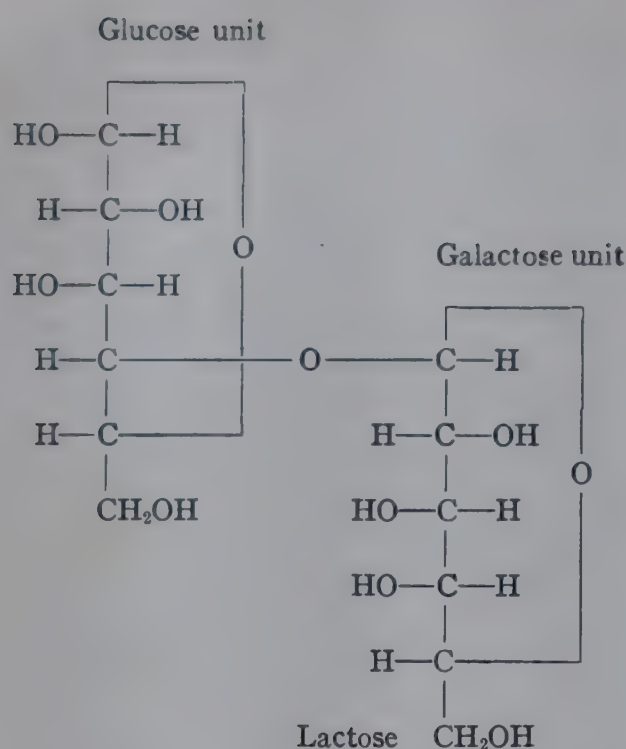
Glucose occurs in the body in combination with other substances. Thus as salts of glucose phosphoric acids, and in the lactating animal in combination with galactose as lactose, which is α - and β -glucose β -galactoside.

Galactose (open chain form)



exists a very small amount of the open chain aldehydic form in equilibrium with the cyclic forms.





The slight difference in chemical configuration between glucose and galactose should be noted. Carbohydrates occur as substituent groupings in certain proteins. Such proteins may be extracted from tissues paying due regard to their solubility properties. From such extracted proteins there has been isolated glucose (from glycoproteins) glucosamine, mannose (from certain blood proteins) and various pentoses that is 5 carbon sugars possessing the general formula ($\text{C}_5\text{H}_{10}\text{O}_5$) in nucleic acid which is combined with certain proteins to give the so-called nucleoproteins (p. 564). It may be pointed out that pentoses also occur in combined form as nucleotides, and that very rarely cases of human pentosuria are encountered.

Carbohydrates also occur linked with fatty substances. Thus the cerebrosides contain within their molecule galactose units. The galactose is present in the normal or amylenic oxidic ring form. Cerebrosides may be extracted with the usual fat solvents. The galactose may be split off from such extracted substances by acid hydrolysis. Glucose may also be present in cerebrosides (p. 597).

METHODS OF ESTIMATION:

Glucose. The simple sugars have three properties which permit their identification and estimation (1) their ability to reduce the salts of heavy metals in alkaline solution (2) their optical activity (3) fermentation by yeast and by various microorganisms. The methods depending on the reduction of the salts of heavy metals have been of great value in physiological work but since other compounds present in the body also possess this property it is necessary to prove that the reduction is due to glucose. This is accomplished by utilizing the third property mentioned above, i.e.,

by fermenting the glucose with yeast or with certain microorganisms. The optical activity of the carbohydrates is an invaluable property when they are present in solutions uncontaminated by various other optically active substances which are present in physiological fluids.

Glycogen. Glycogen is very resistant to alkaline hydrolysis, but, as Claude Bernard discovered, readily yields reducing sugar on acid hydrolysis. Pflüger boiled glycogen for several weeks in strong alkali without destroying it. Advantage is taken of this property to free glycogen of contaminating substances. After alkaline hydrolysis of the tissue the glycogen is precipitated from solution by alcohol. This material is then broken down by acid hydrolysis to glucose, which is stable in acid solution. The sugar is then estimated as described above and the amount of glycogen calculated from the result. There is no accurate method of estimating glycogen as such.

Lactic acid. In muscle, glycogen is broken down to lactic acid during muscular exercise and in the recovery from exercise part of it is resynthesized to glycogen. The lactic acid is estimated by oxidation to acetaldehyde and the latter is determined by distilling it into sodium bisulphite with which it forms a double compound. Residual unbound bisulphite is titrated with iodine.

APPROXIMATE DISTRIBUTION OF CARBOHYDRATES:

	Liver per cent	Muscle per cent	Blood per cent
Glucose.....	0.06- 0.15	0.02-0.04	0.08-0.11
Glycogen.....	0.2 -10.0	0.2 -1.8	trace
Lactic acid...	0.01	0.01	0.01

Liver is 3.3 per cent, muscle 50 per cent and blood 8 per cent of body weight. Glucose and lactic acid are found in the other soft tissues and some of these contain small amounts of glycogen. The glycogen content of kidney and of heart muscle has been extensively studied under various physiological and pathological conditions.

ABSORPTION OF SUGAR

The monosaccharides formed during digestion are rapidly absorbed from the small intestine. In the rat, galactose disappears from the intestine most rapidly, glucose a little more slowly and fructose much more so. There is, therefore, a selective action of the intestinal cells in the absorption of sugars (Cori). Evidence is accumulating that the absorption of sugar may proceed against a concentration gradient i.e. when the concentration is lower in the lumen of the small intestine than in the blood. There is an increase in the amount of esterified phosphate in the intestinal mucosa dur-

ing the absorption of both glucose and fructose but this phosphorylation may be related to metabolism rather than to absorption. It has, however, been suggested by Lundsgaard that the relatively high level of esterified phosphate in the intestinal mucosa during the absorption of fructose may be due to slow dephosphorylation and thus account for the well known delay in the rate of absorption of this sugar.

The slow absorption of glucose from the small intestine after hypophysectomy or adrenalectomy may be a part of the picture of inanition rather than a result of the loss of a specific adrenal phosphorylating factor, as has been suggested. The fact that the administration of sodium salts restores the rate of glucose absorption in adrenalectomized animals (Deuel) is in favor of the non-specific effect.

Glucose is not absorbed in appreciable amounts from the stomach until high concentrations are reached, and only slowly from the large bowel.

THE FATE OF INGESTED OR INJECTED GLUCOSE

There is good evidence that no other monosaccharide is as effective in the liverless animal as glucose. This finding suggests, and there is indeed good evidence, that the other monosaccharides are normally changed to glucose in the liver. Fructose is a better glycogen former than glucose but galactose is much inferior in this respect. When glucose is absorbed or is injected some of it can be accounted for by the increase in liver glycogen, some is converted to muscle glycogen and some is oxidized. The concentration of glucose in the soft tissues is temporarily raised.

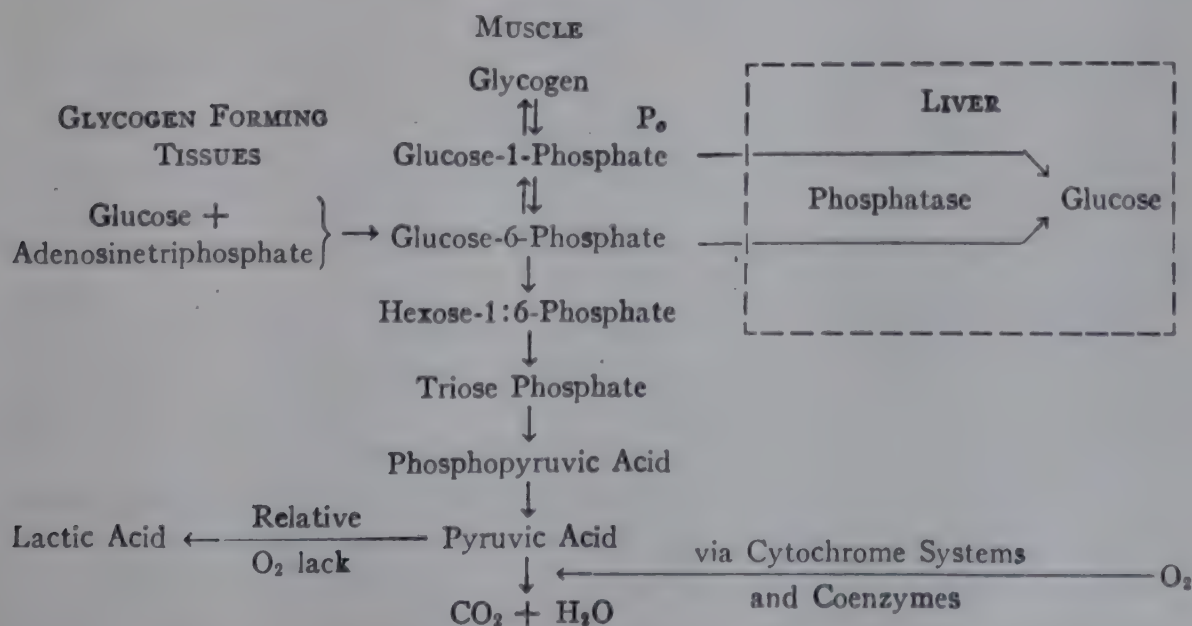
THE FORMATION OF GLUCOSE IN THE BODY

Glucose is apparently formed in appreciable amounts only in the liver. When this organ is removed (Mann and Magath) hypoglycemia soon appears and sugar must be provided if the animal is to survive more than a few hours. Sugar is made from protein in the liver and evidence obtained on phloridzinized animals indicates that some of the amino-acids, glycine, alanine, cystine, aspartic and glutamic acids may yield glucose in the theoretical amounts (Lusk). It is well established that plants form sugar from fat and this possibility must be considered in animals. Direct evidence for this conversion is not available in animals. There are a certain number of reports of respiratory quotients below 0.7 which disturb those who believe in the unitarian significance of the quotient, but this ratio should not be used as a weapon against itself. If sugar formation from fat does take place, all the evidence suggests that the liver is the principal site of the change.

A discussion of the indirect evidence in favor and against the conversion of fat to sugar will not be attempted here. See Lusk "The Science of Nutrition", Macleod "The Fuel of life", and the more recent reviews by Soskin, who summarizes evidence in favor, and by Stadie, who believes this change does not take place in animals.

FORMATION AND BREAKDOWN OF GLYCOGEN AND THE OXIDATION OF SUGAR

Great advances in our knowledge of the most fundamental aspects of carbohydrate metabolism have been made in recent years. Most of the steps in the formation and breakdown of glycogen

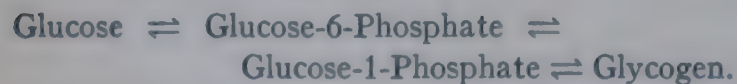


Formation and Breakdown of Glycogen and Oxidation of Carbohydrate

and the oxidation of sugar have been revealed by the work of Harden, Young, Embden, Meyerhof, Warburg, Cori, Lohmann, Peters and numerous other investigators. Many of the individual steps are not observed in the intact cell since the intermediate products which have been identified "in vitro" do not accumulate. There are, for example, some twelve enzymatic reactions involved in the anaerobic conversions of glycogen to lactic acid. Practically all of these have been shown to be reversible but since the final product of one reaction is immediately removed by the following step the process proceeds in one direction. The phosphorylation of glycogen and of glucose has been proved to be the introduction to a long series of changes by which these products are transformed through various phosphate esters to pyruvic or lactic acid. Glycogen after phosphorylation breaks down to glucose-1-phosphate. This (Cori ester) is converted to glucose-6-phosphate which is also the first step in the oxidation of glucose.

The work of Cori and Cori in which the enzyme phosphorylase, which catalyses the reversible reaction glycogen (or starch) + inorganic phosphate \rightleftharpoons glucose-1-phosphate, was isolated and purified is of great interest. This enzyme is widely distributed in animal tissues and is responsible for the first stage in the breakdown of glycogen. It also affects the synthesis of a polysaccharide indistinguishable from glycogen. Some glycogen must be present to "prime" this latter reaction and adenylic acid is an essential constituent of the mixture for activity in either direction. It is of significance that one of the fundamental reactions of carbohydrate in the animal body glycogen \rightleftharpoons glucose can be demonstrated in the test tube in the absence of any of the hormones which affect the rate of this reversible change under physiological conditions.

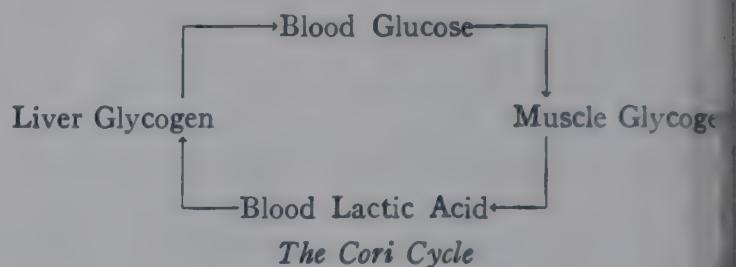
It may be emphasized again here that the intermediate steps between glycogen and glucose are phosphorylated compounds.



It is now well established that this transfer of phosphate groups is of paramount importance in the mechanism by which cells derive energy from the breakdown of food materials. Muscle glycogen breaks down to CO_2 and H_2O under physiological conditions. The steps from glycogen to pyruvic acid can occur anaerobically but from pyruvic acid on, an adequate oxygen supply is necessary. When there is a relative lack of oxygen

lactic acid is formed. This lactic acid may diffuse out into the blood stream and it is then converted in the liver to glycogen.

This part of the so-called Cori cycle is apparent not brought into play under ordinary circumstances but is involved in muscular exercise and under conditions of anoxia.



Glycogen-containing tissues, with the exception of the liver, exhibit the same pattern of breakdown of this polysaccharide as has been described in muscle. In the liver, glycogen does not normally break down to CO_2 and H_2O or to lactic acid but to dextrose. This is probably due to the fact that the liver contains a very active phosphatase which converts the glucose-1-phosphate and the glucose-6-phosphate to glucose and thus removes these esters from the medium.

Under certain conditions, *in vitro*, glyceric aldehyde phosphate and dihydroxyacetone phosphate can be isolated from the breakdown products of muscle glycogen. In the diabetic dog these substances, and also pyruvic acid, form "extra sugar" but so does methyl glyoxal which is not a part of the accepted schemes. In the living organism it is impossible to decide at present whether these substances, when administered, are used instead of glucose or are actually converted to glycogen or glucose before utilization. The use of appropriate tracer substances may help to solve these problems.

THE REGULATION OF BLOOD SUGAR

The blood sugar level represents the resultant of oxidation, storage and excretion on the one hand and formation and absorption on the other. This may be represented graphically.

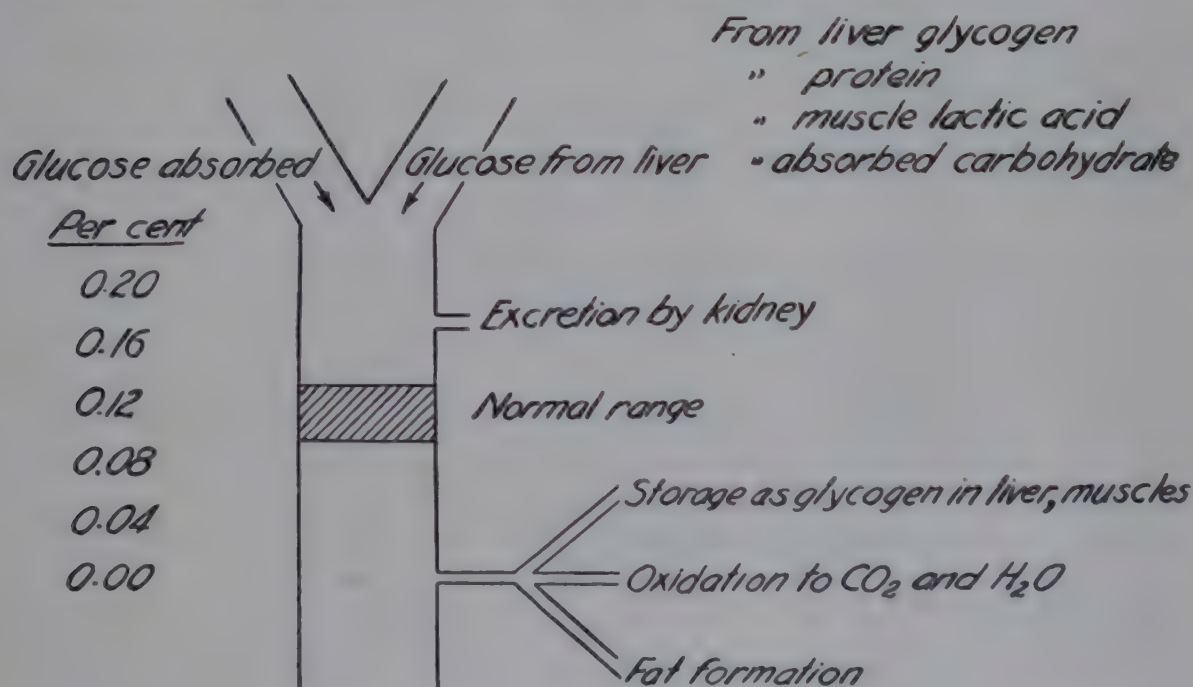
The relative constancy of the blood sugar which is an equilibrium mixture of α and β glucose in the normal fasting animal is made more remarkable by the fact that the production, storage, and utilization of sugar are affected by a great number of chemical and nervous factors.

When sugar is not being absorbed from the intestinal tract it must be made in the liver from non-carbohydrate sources or liberated by the breakdown of liver glycogen. The liver glycogen is the emergency supply which is available while

the process of gluconeogenesis is gathering speed. In the average man approximately 100 gms. of glycogen are present in the liver and this would only supply the demands for sugar for some five hours if the gluconeogenesis were to cease. The rate of glycogen breakdown is affected by adrenaline which is liberated in emergencies, and the rate of gluconeogenesis by the internal secretions of the anterior pituitary gland, the adrenal cortex, the thyroid and the pancreas, as will be discussed later. An important part of this homeostatic mechanism for the regulation of blood sugar appears to be the level of blood sugar itself (Soskin). Under experimental conditions in which variation in the rate of secretion of insulin is impossible, i.e. in the depancreatized dog given insulin at a constant rate, indirect evidence indicates that the administration of dextrose decreases the rate of output of sugar

production in an excessive rate of discharge of sugar from the liver. Disturbances in endocrine function are the main causes and the mechanism of these changes will be discussed later.

Transient hyperglycemia may be due to either physiological or pathological processes. Alimentary hyperglycemia is a physiological process and its height depends on the amount and nature of the carbohydrate in the meal. Adrenaline hyperglycemia is a part of the physiological response to an emergency. Nerve impulses acting on the liver, changes in hydrogen-ion concentration of liver cells due to asphyxia or other causes, may produce a transient rise in blood sugar. Toxic products of infection acting on the liver to increase gluconeogenesis or on tissues in general to diminish utilization of sugar may produce a hyperglycemia of short or long duration.



by the liver. In the intact animal the pancreatic mechanism is also involved. The insulin content of the blood probably determines at what level of blood sugar gluconeogenesis in the liver will be inhibited. In the absence of insulin there is no evidence that any level of blood sugar inhibits the new formation of sugar.

HYPERGLYCEMIA

An increase in the blood sugar beyond the normal range constitutes a hyperglycemia. This is a protective phenomenon. With the exception of insulin a rise in blood sugar provides the greatest single stimulus for the formation of glycogen and the utilization of glucose.

Prolonged hyperglycemia may be present when either or both of the following processes are operating (1) diminished utilization of glucose, (2) over-

PANCREATIC DIABETES

Removal of the pancreas

When the pancreas is completely removed from a dog or cat, a characteristic syndrome rapidly develops (Mering and Minkowski, 1889). When a diet including the known essentials is provided, the animals may live indefinitely if adequate amounts of insulin are administered. The animals recover rapidly from the operation and appear normal, but the diabetic state quickly supervenes when insulin is discontinued. The sugar content of the blood begins to rise within a very short time, depending on the size of the last dose of insulin, and increases from the normal level of 0.08–0.11 per cent to 0.20–0.40 or higher within twenty-four hours. The urine gives a positive Benedict's qualitative test for sugar when the

blood sugar rises above approximately 0.16 per cent. This point, the so-called renal threshold, is the level of blood sugar above which large amounts of sugar are excreted in the urine. In some animals the "threshold" rises when the diabetic state is allowed to persist. (There is some glucose in normal urine and small amounts of other sugars.) The excretion of nitrogen is increased and this may be taken to indicate protein breakdown. The ratio of glucose to nitrogen excreted in phloridzin poisoning is 3.6:1 but this ratio is not observed in depancreatized dogs and indeed that obtained is so variable that little significance can be attached to it. The ratio is low in animals on a high protein diet and there is evidence that the addition of fat may increase it somewhat. It is established that glycerol may be converted to sugar. In the fasting diabetic the blood sugar and sugar excretion are maintained at high levels. The sugar is apparently formed from body protein in the liver since the blood sugar of the diabetic falls rapidly after hepatectomy. The loss of protein contributes to the decrease in body weight.

The disturbed metabolism of fat in the depancreatized animal is indicated by the accumulation of the ketone bodies in the blood and by the excretion of excessive amounts in the urine. The ketosis in a fat dog is greater than in a lean, but this species is characterized by its efficiency in metabolizing fats, without ketosis. The loss of body fat is rapid but the ketosis may be so severe, even in this species, that the animal dies in coma before the fat reserves are depleted.

β -hydroxy-butyric and aceto-acetic acids and others derived from tissue breakdown appropriate base and thus when the available reserve of base is depleted may produce an acidosis. In acidosis the respiratory center is stimulated and "air hunger" and coma are produced. The exact mechanism of coma production in diabetes is not known. Some observers believe that aceto-acetic acid is particularly toxic. This acid is oxidized in the bladder and lungs to form acetone, which is excreted in the urine and expired air.

The neutral fat content of the blood increases due probably to the increased rate of mobilization of depot fat and there is also a rise in cholesterol esters and the phospholipid.

Very few authorities will deny that the evidence for the increased rate of production of sugar from protein in pancreatic diabetes is satisfactory. While there is an abundance of evidence that the depancreatized dog can still burn sugar—all the

criteria of sugar combustion in the normal have been satisfied—it is not permissible to conclude that there is not some interference with the process. The rapid sugar utilization in the hepatectomized diabetic animal and the production of the diabetic condition by the administration of the diabetogenic substance of the anterior pituitary which apparently acts, in part, by stimulating the liver to produce more glucose, tend, however, to emphasize over-production rather than under-utilization. On the other hand the anterior pituitary contains substances which inhibit the utilization of glucose.

The respiratory quotient of the depancreatized animal not receiving insulin assumes the low level 0.69–0.73 and is not usually raised when sugar is given. Under certain conditions, in animals which have received a high protein diet and insulin, for a time the quotient may be higher (Soskin). The characteristic low quotient may indicate combustion of fat but if any process, such as conversion of fat to sugar which gives a very low quotient, should be taking place the ratio might indicate the resultant between sugar combustion, fat combustion, and the conversion. In brief, since more than one interpretation of a quotient is possible great caution must be observed in drawing conclusions with regard to its significance. When the liver is removed from a depancreatized dog the quotient rises, indicating either that relatively more sugar is being burned or that conversions giving a low quotient are taking place to a smaller extent.

The glycogen content of the muscles of a depancreatized animal may be reduced below the normal level, but appreciable amounts remain. There is no diminution of heart muscle glycogen and recently convincing evidence of an increase has been obtained. Liver glycogen falls to very low levels. A slight increase in both muscle and liver glycogen can be produced by giving large amounts of sugar without insulin.

While the glucose utilization of the normal heart is low, that of the diabetic animal is even less when the blood sugar concentrations are the same. Lactate, however, is used almost as well by the diabetic as by the normal heart (Lovatt Evans). These findings eliminate the necessity of supposing that the diabetic heart depends for its energy entirely on protein and fat. The rate of usage of glucose but not of lactate by the diabetic heart is increased when insulin is supplied (see also p. 267).

The excretion of phosphorus is increased in the depancreatized animal. The administration of

sugar or adrenaline does not cause the prompt fall in the inorganic phosphate of the blood which is observed in normal animals. These substances, therefore, produce their effects by raising blood sugar which in turn calls forth insulin, or reduces the rate of sugar production by the liver. Adrenaline and insulin thus affect blood inorganic phosphate similarly.

The diabetic animal is very susceptible to infections but it is not established that this is due to the raised sugar content of the tissues. The specific antibodies are not significantly altered in amount but other defence mechanisms may be made less effective by the abnormal metabolic condition

and exhibit only a mild form of diabetes. Severe diabetes produced under these conditions by administration of the diabetogenic substance of the anterior pituitary is alleviated by insulin.

THE ANTIDIABETIC HORMONE—INSULIN

The name *insuline* was suggested by de Meyer in 1909 for the hypothetical internal secretion of the pancreas the search for which had been stimulated by von Mering's and Minkowski's findings (1889). While other workers, among whom Hédon, Zuelzer, and Scott may be mentioned, obtained very suggestive results, which in some cases were probably due to the presence of insulin, Banting

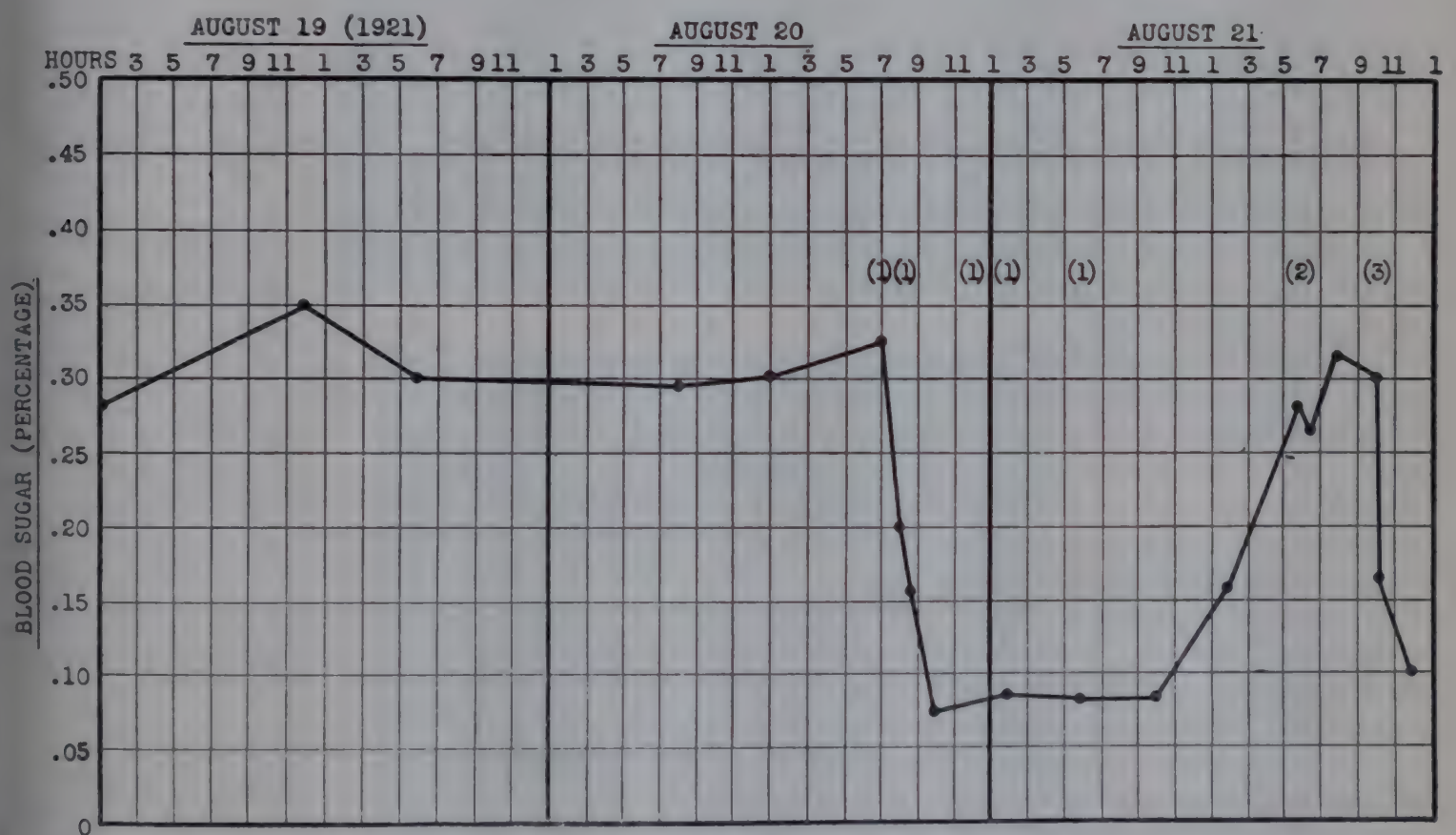


FIG. 232. Effect of insulin on the blood sugar curve of a depancreatized dog (redrawn from Banting and Best). (1) Injection of extract of degenerated pancreas; (2) extract after incubation with pancreatic juice; (3) extract incubated without pancreatic juice. Blood sugars by Myers-Bailey modification of Lewis-Benedict method.

which exists. Pathological conditions are observed with considerable frequency in the eyes of diabetic animals. The liver rapidly undergoes extensive fatty degeneration and there may be an accumulation of large amounts of neutral fat (p. 1012).

While there is considerable variation in the length of life of the depancreatized dog or cat, most individuals fed on a mixed diet do not live for more than two or three weeks without insulin. Under certain conditions dogs may survive for seven weeks. It is now established, however, that when the anterior pituitary is also removed the animal (dog) may live for nine months, at least,

and Best working in Macleod's laboratory (1922) were the first to obtain a preparation containing the antidiabetic hormone in a form which consistently alleviated all signs of diabetes in completely depancreatized dogs (fig. 232).

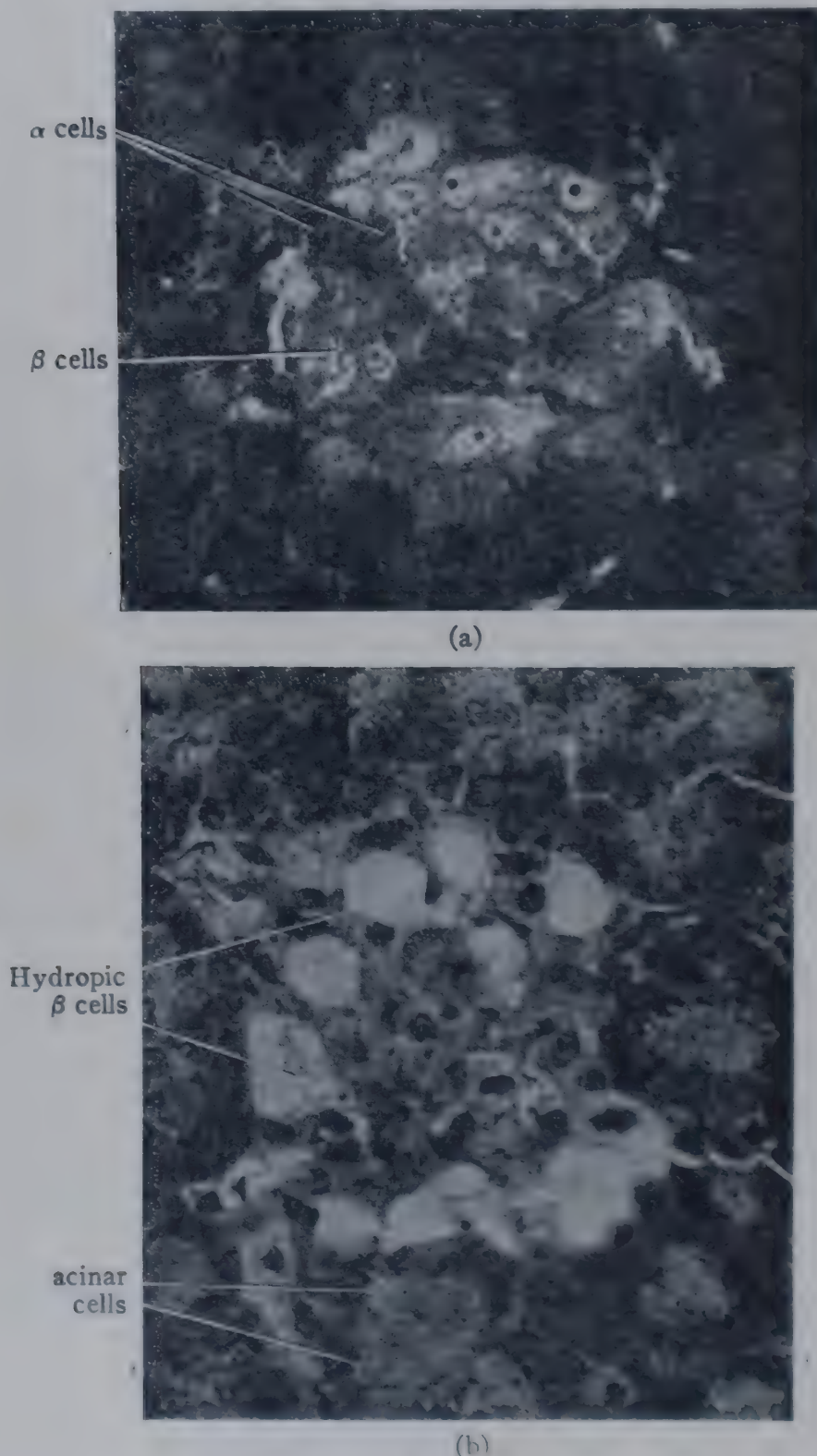
SOURCE OF INSULIN

While it is reasonable to suppose that small amounts of insulin are present in tissues other than the pancreas, methods are not yet available for their estimation. Blood provides an exception to this generalization but the active substance is detected by the intravenous administration of the whole blood and not by extraction of the insulin

from the tissue. A reliable procedure for the determination of insulin in blood would unquestionably result in great advances in our knowledge of carbohydrate metabolism. Gellhorn and his associates, among others, have recently suggested

the only organ to manufacture insulin or to store it in more than minute amounts.

The islet cells of the pancreas are of four types— α , β , γ and δ . The α and β types contain granules. The γ are non-granular. The δ cells have



(b)
FIG. 253

(From Ham and Haist)

(a) Normal Islet, stained by the method of Bowie.

(b) Hydropic Islet, stained with Haematoxylin and Eosin.

methods based on the susceptibility to insulin of small animals from which the adrenal medulla and pituitary glands have been removed. Much further work is required in this field. In the mammalian organism the pancreas appears to be

been seen only in human pancreas (Bloom) and are not well defined. In dog pancreas the number of cells per islet varies greatly, as do the relative numbers of the various types of cells. One study gives the average number per islet as 30 and the

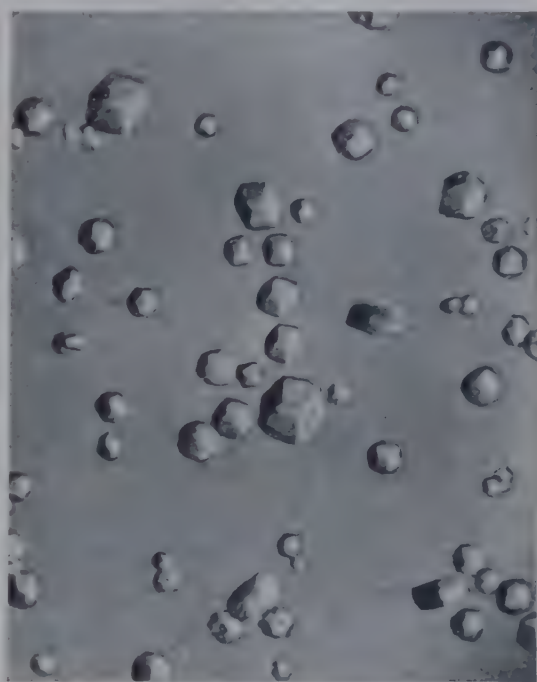
verage ratio of α to β cells as 20:75. The islet volume may be about one one-hundredth of the pancreas. The β cells occupy the periphery of the islets and are smaller than the others. It is these β cells which are considered to be producers of the antidiabetic hormone; indeed, the granules of these cells may consist largely of this substance. Epithelial cells of the small ducts are considered to be the "mother cells" of the islet and acinar cells. New islet cells may, therefore, be produced from them.

The main points of evidence which indicate that the hormone is produced in the islet cells are as follows: 1. Histologically, the islets are glandular structures, the obvious outlet for the secretion of which is through the blood stream. 2. There are relatively large amounts of the hormone in the principal islets of teleosteal fishes, in which few enzyme-producing cells are found. 3. The active substance is found in degenerated pancreas in which the loss of acinous tissue has proceeded more rapidly than that of the islet cells. Ligation of the pancreatic ducts eventually produces a decrease in the insulin content of the pancreas, but moderate amounts of insulin may still be extracted when very few enzyme-producing cells remain. 4. When most of the pancreas, approximately nine-tenths, is removed from a dog, characteristic lesions (hydropic degeneration) are found in the β cells of the remnant. These changes can be accelerated by a high carbohydrate diet, and prevented or eliminated by administration of insulin or by fasting. 5. The clinical condition known as hyperinsulinism occurs when the pancreas liberates abnormally large amounts of antidiabetic hormone. In many of the cases there are definite tumors of the islet cells. After operative removal of these masses of islet cells the blood sugar is maintained at higher levels. 6. Metastases in other tissues arising from carcinoma of the islet cells have been shown to contain insulin. 7. The injection of anterior pituitary extracts leads to destructive changes in the islet cells, chiefly in the β cells, while there is little or no effect on the α cells. The pancreases from a number of dogs treated with these extracts have been assayed for their insulin content, and the values obtained were roughly proportional to the concentration of granules in the β cells as determined by histological studies of these tissues, using Bowie's staining technique.

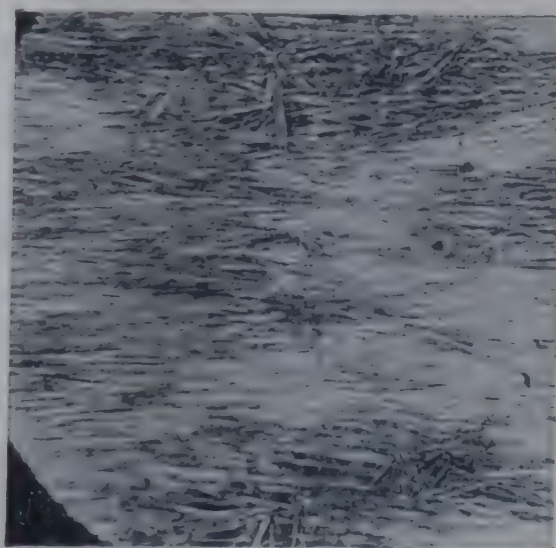
CHEMISTRY OF INSULIN

Insulin was first obtained in crystalline form by J. J. Abel and his colleagues in 1926. In 1934

D. A. Scott showed that the crystalline material was the salt of insulin with a metal such as zinc, cobalt, cadmium or nickel. The active material is a protein. It may be regarded as an albumin. By the Svedberg ultracentrifuge method it has a molecular weight similar to that of egg albumin, namely, 35,000. It now can be readily crystallized, usually in the form of twin rhombohedra of microscopic size, at a hydrogen-ion concentration



Zinc Insulin Crystals



N-amylamine Insulin Crystals
(Kindness of Dr. D. A. Scott)

FIG. 234

a little above its isoelectric point (pH 5.2), provided salts of zinc, nickel, cadmium or cobalt are present in the solution. These metals are evidently linked chemically with the protein in its crystalline state, for they occur in constant amounts and these amounts are proportional to their atomic weights. Zinc is present in zinc insulin crystals to the extent of nearly 0.5 per cent. The fact that normal pancreatic tissue is relatively

rich in zinc may be of some significance in the storage of the hormone in the gland. The protein has a high sulfur content (3.2 per cent), all present in the form of cystine. The molecule contains no carbohydrate material, and apart from its low mineral content, appears to be wholly constituted of amino acids. The constituent amino acids and their percentage distribution are as follows: serine 3.6, threonine 2.7, glutamic acid 21, cystine 12.9, leucine 30, lysine 1.3, arginine 3.3, histidine 4, phenylalanine 8.4, tyrosine 12.8, proline 10.

Slightly acidified insulin has been kept for long periods, but in dilute alkali insulin is relatively unstable. It is hydrolyzed and so is rendered physiologically inactive by those enzymic preparations which attack proteins. Thus, trypsinogen is without effect on insulin, and a portion of pancreas may be incubated at 37 C. for some hours without any alteration in the amount of insulin which can be extracted from it. Various attempts have been made to ascertain if there is in the molecule a specific grouping of certain of the amino acids which is really responsible for its hormonal activity. It may be concluded that the physiological activity of insulin may be slightly and sometimes reversibly decreased by certain minor chemical changes in the molecule, whereas appreciable chemical alteration gives a considerable diminution or complete absence of activity. These considerations are linked with the fate of insulin in the animal body after secretion from the pancreas or after parenteral injection. Proteases of the blood and other tissues may effect considerable destruction. Other changes have been suggested, such as the action of sulfhydryl groupings, as in glutathione, which may reduce the cystine disulfide linkage, a change which is known to be accompanied by inactivation.

STANDARDIZATION

Zinc insulin crystals from all sources so far examined (man, cattle, hog, sheep, bison, fish) have the same potency. Very recently, preparations of zinc insulin crystals have been made of slightly greater potency than usual. This work may have considerable theoretical interest. The international standard, a preparation of zinc insulin crystals, is defined as containing 22 units per milligram. There are two well established methods of assaying the potency of an insulin preparation. The lowering of blood sugar in fasting rabbits and the production of convulsions in fasting mice both furnish satisfactory effects of insulin for the comparison of unknown and standard products.

LIBERATION OF INSULIN

The arrangement of the capillary loops about the islet cells and the reported scarcity of lymph channels provide morphological evidence in favor of the capillary blood stream as the pathway by which insulin reaches the systemic circulation. It is important to remember that insulin passes first to the liver.

While there are many pieces of experimental evidence which support the conclusion that the level of blood sugar is an important factor in the regulation of insulin liberation, the possibility that a decrease in the rate of discharge of sugar from the liver may also be produced when the blood sugar is raised, is frequently overlooked.² This latter effect is apparently produced by a direct action on liver cells. The injection of small amounts of glucose into the artery supplying a pancreas grafted into the neck of a depancreatized dog or into the pancreatic artery in a decerebrate cat causes a prompt lowering of blood sugar. In the latter case the effect was not obtained when the splenic or portal vein was used. If these results can be accepted they provide evidence for the chemical control of insulin liberation through the action of the glucose on structures within the pancreas. The results of experiments with denervated pancreatic grafts indicate that the nervous control is not essential. The nerve impulses which affect the islet cells are apparently conducted by the vagus. Vagus fibres have been traced to the islet cells and non-medullated branches are said to pierce them. The results of stimulating the vagus *appeared* to be clear cut and the pathway was traced by one group of investigators to the hypothalamic region, but other workers have as yet been unable to confirm these findings.

Information on the factors controlling the secretion of insulin has accumulated very slowly. The finding of Houssay, Foglia and their collaborators that two or three pancreases from normal dogs, when introduced into the carotid-jugular circulation of a depancreatized dog, produce no more effect than one pancreas, is strongly indicative of a chemical control of insulin liberation. These workers have studied the rate of liberation of insulin from the pancreas of hypophysectomized dogs, and of dogs made transiently or permanently diabetic by anterior pituitary extracts. The findings in general conform to those obtained by

² There may be a constant liberation of a small amount of insulin.

studying the insulin content of pancreas in relation to the state of carbohydrate metabolism of the animal (p. 584). Neither of these methods yields information as valuable as that which will be obtained when the insulin content of blood, and the rate of pancreatic blood flow can be accurately determined in intact unanesthetized animals.

GENERAL EFFECTS OF INSULIN ON THE DIABETIC ORGANISM

It is well established that insulin restores to the depancreatized animal its ability to utilize sugars and fats in a normal manner. The excessive breakdown of protein is prevented. The ketosis rapidly disappears. Glycogen is deposited in large amounts in the liver. Muscle glycogen may be increased. The respiratory quotient rises when sugar is made available, or in fact when insulin alone is administered. Animals recover their ability to deal with infective agents. In brief, a well-treated depancreatized animal is difficult to distinguish from a normal one. There has been the difficulty, of course, that in the animal without a pancreas relatively large amounts of insulin are made available (by subcutaneous or intravenous injection) while in the intact animal small or large amounts are presumably liberated from the pancreas as the need arises. Adult depancreatized dogs on an adequate diet including the enzymes of the external secretion of pancreas have been maintained in good condition for more than four years (Macleod; Hédon; Bliss; Fisher).

THE MECHANISM OF ACTION OF INSULIN

In both the diabetic and the normal animal the level of blood sugar is lowered by the administration of insulin. The diabetic animal is more susceptible to insulin than the normal. In both the normal and the diabetic individual the oxygen consumption is increased and the R.Q. rises. This indicates that more sugar is burnt when insulin is provided. Small amounts of glycogen may be deposited in the muscles and liver of the depancreatized dog when no insulin is given but the administration of insulin produces a dramatic increase in the rate of glycogen deposition in both these tissues. In the normal animal one of the most clear cut effects of insulin is the increase in the rate of glycogen deposition in the muscle which it produces but it has not been demonstrated in any normal adult animal that insulin increases the level of liver glycogen. The increase seen in the livers of young rabbits is due to a secondary liberation of adrenaline. In the normal adult animal

there may be an actual loss of glycogen from the liver when insulin is administered. This is due to the accelerated glycogen deposition in muscle and the increased rate of oxidation of sugar.

There is now convincing direct evidence secured by the use of thermostromuhr technique for measuring blood flow to the liver and by blood sugar estimation, that the injection of insulin decreases gluconeogenesis in the liver. It will be appreciated that it was necessary to determine the blood flow as well as the concentration of sugar in the blood going to and flowing away from the liver before this fact could be established. One of the main effects of insulin, therefore, is exerted on the liver. It will be remembered that this tissue has first opportunity to utilize the supply of insulin which is secreted by the pancreas into the pancreatic capillaries and veins and thence by way of the portal system to the liver. It is also significant that the liver is responsible for a very large fraction of the total metabolic changes which take place in the body.

Insulin is, however, effective in the hepatectomized animal. In this preparation or in one from which all the abdominal viscera has been removed, the administration of insulin increases the deposition of muscle glycogen and the oxidation of sugar. In balanced experiments these two processes account satisfactorily for all the sugar which disappears. The action of insulin can also be demonstrated on the perfused leg of the cat or dog and it has now been shown that in the surviving diaphragmatic muscle of the rat suspended in oxygenated Ringer's solution containing glucose, the rate of formation of glycogen is increased when insulin is added to the solution. No effect of insulin on the oxygen consumption of this preparation has been demonstrated.

The addition of insulin delays the falling-off in respiration of minced pigeon-breast muscle and this effect can be demonstrated even without the simultaneous addition of citrate which was originally thought to be necessary. A greater effect was found when the muscles from depancreatized pigeons were used. This action has not yet been demonstrated in mammalian muscle. Insulin has been found to stimulate the respiration of baker's yeast under certain conditions.

In the depancreatized animal insulin decreases the lipemia and cholesterolemia and prevents the deposition of the large amounts of excess fat which accumulate in the liver in the untreated animal. The level of the ketone bodies in the blood is restored to normal. This effect may be due to a

diversion of metabolism from fat to carbohydrate. The formation of fat from carbohydrate is increased under the influence of insulin. It has been shown that insulin in the presence of fructose fumarate or lactate inhibits the formation of ketone bodies in liver slices of diabetic cats.

The excretion of nitrogen in the diabetic preparation is decreased by the administration of insulin. In the normal or diabetic animal the amino acids, urea, creatine and creatinine content of the blood are decreased by insulin administration. This effect which may be in part due to the secondary liberation of adrenaline, is also a direct action of the antidiabetic hormone. It has been reported that insulin increases the rate of utilization of amino acids by the muscles and that the synthesis of protein is accelerated. Undoubtedly a large part of the effect of insulin on protein metabolism, is due to a decrease in the rate of gluconeogenesis in the liver.

Insulin decreases the inorganic phosphate of the blood and there may also be a slight increase in the hexose phosphate content of muscle but this latter effect is due, in part at least, to a secondary liberation of adrenaline during the insulin hypoglycemia.³

Various changes in the concentration of the metallic constituents of the blood have been reported after insulin injection. These, and particularly that in the concentration of potassium, suggest a fundamental relationship between electrolyte and carbohydrate metabolism. The decrease in blood sugar produced by insulin is accompanied by a simultaneous fall in potassium.

It is now well established that the administration of insulin lowers the insulin content of the pancreas in fasting or fed animals. Furthermore it protects the islet cells against the degenerative changes which occur after the removal of a large part of the pancreas. Similarly the degenerative changes in the islets and the loss of insulin content produced by the administration of the diabetogenic substance of the anterior pituitary gland are prevented if insulin is supplied. If, after the diabetic state has been produced in partially depancreatized dogs by administration of diabetogenic preparations, insulin is given in adequate amounts, the diabetes may disappear. Thus insulin under these experimental conditions can both prevent and cure diabetes (Haist, Campbell and Best; Lukens and Dohan).

³ There is some evidence that the rate of turnover of certain of the phosphate compounds in muscle and the amount of adenosine triphosphate in liver may be increased by insulin.

As we have stated previously, small amounts of muscle glycogen may be deposited in the diabetic organism in the absence of insulin. When insulin is provided the rate of deposition of muscle glycogen is greatly accelerated. Insulin enables the body to effect this conversion at physiologic concentrations of blood or tissue sugar. It is of great interest, as mentioned previously, that the *in vitro* conversion of glucose to glycogen may be effected in the absence of insulin and that the addition of insulin exerts no effect. It follows from this finding that insulin may exert its effect on carbohydrate metabolism at some intermediate step between the hexose phosphate and the pyruvic acid. The dependence of the glycogen forming enzyme, phosphorylase, on the concentration of inorganic phosphate may be emphasized again here. Reactions which lower the concentration of inorganic phosphate i.e. the action of insulin, should stimulate phosphorylase activity in the direction of glycogen synthesis.

INTERFERENCE WITH THE ACTION OF INSULIN

Other hormones. There are five internal secretions the action of which may be considered to be antagonistic to that of insulin. There is no evidence of any chemical interaction of these hormones with the antidiabetic substance.

Enzymes. Insulin is destroyed by pepsin-HCl and by the activated proteolytic pancreatic enzyme. Pancreas may, however, be incubated aseptically at neutral or acid reaction without loss of the antidiabetic substance. Insulin is relatively unstable in alkaline solution. There is apparently an enzyme system in blood which is capable of inactivating insulin but its characteristics have not been extensively studied.

Reaction of tissues. Since insulin acts on the cells of the liver and muscles, factors which influence these tissues, acidosis for example, may modify insulin action. Furthermore, since the liver is so largely responsible for the regulation of blood sugar, influences affecting this organ may cause a change in sugar content quite apart from the action of insulin. A change in the acid-base equilibrium of the body toward the acid side renders injected insulin less effective, a change toward the alkaline makes insulin more effective.

Products of infection. The toxic products elaborated by many microorganisms may interfere with the action of insulin. There is experimental evidence (1) that the insulin content of pancreas is decreased in certain severe infections but this does not necessarily indicate a decreased rate of

liberation of the hormone, (2) that the suprarenal and thyroid glands are stimulated to release more of their internal secretions,⁴ (3) that the synthesis of glycogen from lactic acid in the liver is inhibited and (4) it now appears that normally liver glycogen is changed to glucose by the phosphorylating mechanisms discussed above. Amylase, which splits glycogen to dextrins, maltose and finally to glucose, does not have access to the liver cells. When certain toxins are administered, however, amylase activity can be demonstrated and this abnormal route of glycogen breakdown provides another mechanism by which the products of infection make the organism resistant to the action of insulin. Insulin has no effect on the activity of amylase. Certain toxins may act on one or more of these mechanisms but investigation of this field is still in the preliminary stages.

Anesthetics. All anesthetics interfere more or less with the action of insulin. More or less asphyxia is produced by all general anesthetics. In asphyxia (1) adrenaline is liberated and (2) acid products tend to accumulate. Chloralose and amytal cause the least disturbance of carbohydrate metabolism.

SUBSTITUTES FOR INSULIN

Insulin therapy has two obvious disadvantages (1) the transient effect and (2) the necessity for parenteral injection of the active material. The most important of the suggested substitutes is synthalin (decamethylenediguanidine). This substance does not increase deposition of glycogen and the effect on hepatic gluconeogenesis is accomplished in a highly unphysiological manner. Insulin is apparently the only agent which inhibits sugar formation without damaging liver cells. Extensive deposits of fat produced in diabetic dogs by fat feeding as well as by many chemical compounds other than synthalin interfere with sugar formation. It is preferable that the human diabetic organism should excrete some of the sugar made by a relatively healthy liver than to be made "sugar free" by damaging liver tissue so that less glucose is formed.

INSULIN REQUIREMENT AND ADMINISTRATION

Interesting studies have been made of the insulin requirements of depancreatized dogs under different conditions. Thus the blood sugar has been

kept at a normal level by simultaneous and continuous intravenous injection of insulin and dextrose solutions. The insulin required was between 0.06 and 0.4 units per kilogram per hour, while the corresponding requirement of dextrose was 0.2 and 0.6 gm. per kilogram per hour. The higher values for insulin and dextrose were those required by unanesthetized dogs; the others by anesthetized dogs. In another study the amount of insulin necessary to keep the blood sugar at a normal value in depancreatized dogs under basal conditions was between 0.005 and 0.035 units per kilogram per hour, with an average value of 0.017 units per kilogram per hour. The duration of action of insulin is not proportional to the size of the dose injected but is a simple function of the logarithm of the dose; i.e., insulin is inactivated in the body at a rate proportional to the amount in the body at the time. Thus if 1 unit lasts four hours, 10 units would last eight hours.⁵

Insulin may be administered effectively by the subcutaneous or intravenous route. Some absorption may be obtained by inunction or by application to the sublingual or other mucous surfaces. Rectal administration is ineffective. Studies continue to be made on the problem of the oral administration of insulin. Efforts have been made to combine it with various materials, dyes, phenolic substances, tannic acid etc. which might protect the protein molecule from destruction by the intestinal enzymes. The difficulties involved are obvious, and it is therefore not surprising that, while some success has attended these efforts in the laboratory, no satisfactory application to the treatment of diabetic patients has yet been made.

MODIFIED INSULIN

One of the most obvious difficulties in the use of regular insulin in clinical diabetes is its transient and sometimes too violent action. This difficulty has been much more frequently encountered since the highly purified preparations of insulin have been made available. The cruder products were absorbed more slowly. While a great many attempts have been made to slow and prolong the action of insulin, the first important success has been obtained by Hagedorn, Jensen, Krarup and Wodstrup. These investigators have shown that a compound of insulin with any one of several protamines exerts a slower and more prolonged

⁵ Several observers have now suggested that the insulin requirement for the completely depancreatized human subject is less than that of many severe diabetics. These studies are difficult to control and final judgment on this important point must be reserved.

⁴ The first effects of the products of infection may be to excite liver tissue to increased gluconeogenesis and discharge of glucose. Later the liver cells may be damaged so that less glucose is produced.

anti-diabetic effect than regular insulin. This has been shown by microscopic observation (Beecher and Krogh) to be due to the much slower absorption of the insulin combined with protamine than is the case with the regular preparations of this substance.

The incidence of hypoglycemic reactions when protamine insulin is used is much less than with regular insulin. The blood sugar level is much more constant and the patient is maintained in a more physiological state. The clinical findings of the Danish group have already been abundantly confirmed.

Completely depancreatized dogs may be maintained sugar free, while receiving a very liberal diet, on one dose of protamine insulin daily without the development of any hypoglycemic reactions (Kerr and Best).

Scott and Fisher have demonstrated that protamine insulin is greatly improved by the addition of a small amount of zinc. The resulting product, protamine zinc insulin, exerts a more prolonged hypoglycemic action and forms a much more stable suspension than protamine insulin. In the United States and Canada about 55 per cent of the total insulin used is now in the form of protamine zinc insulin.

Various other forms of modified insulin have been prepared and tested clinically. Histone insulin and globin insulin are examples. Clinical opinion is still largely in favor of protamine zinc insulin.

HYPOGLYCEMIA

Under certain exceptional circumstances hypoglycemia may be produced by excessive utilization of glucose (prolonged very violent muscular exercise) but interference with the formation of sugar in the liver is largely responsible for most types. The three main factors which diminish sugar production may be classified as follows: (1) abnormality of liver cells, (2) the inhibiting action of insulin on gluconeogenesis in the liver, and (3) the decreased hepatic gluconeogenesis resulting from diminished output of the anterior pituitary, thyroid, or cortical and medullary adrenal secretions. Under the first heading a great variety of experimental and clinical conditions may be listed—for example—phosphorus or hydrazine poisoning, yellow fever, acute yellow atrophy, and the bacterial infections. When the normal liver is completely removed, profound hypoglycemia occurs promptly. Approximately 80 per cent of the normal liver must be removed before hypoglycemia

is produced. Under the second heading we now consider *hyperinsulinism*. This term should be reserved for conditions in which it is established that there is liberation of excessive amounts of insulin from the pancreas. This has been the case in numerous instances in which the removal of a tumor of islet cells has corrected the hypoglycemia. Correction of the condition by removal of a large part of the pancreas does not prove that the cause was liberation of abnormal amounts of insulin since decreasing the amount of insulin may merely compensate for the first abnormality. Insulin as discussed above causes hypoglycemia by other mechanisms as well as by decreasing gluconeogenesis. The relative importance of the three glands of internal secretion listed under the third heading may vary in different species. Removal of the thyroid increases the sensitivity of an animal to insulin and the same is true of the adrenal medulla, but hypoglycemia is not produced. When the anterior pituitary is extirpated, however, there may be profound hypoglycemia and this finding suggests that diminished secretion of the diabetogenic substance may be an important factor in certain clinical cases in which the liver and pancreas appear perfectly normal. In some species removal of the whole adrenal gland causes hypoglycemia and this is, at least partially, corrected by the administration of cortical extract. Clinically certain cases of Simmond's disease (diminished anterior pituitary secretion) and of Addison's disease (involvement of adrenal cortex) may exhibit hypoglycemia. (See table 55.)

Signs and symptoms

The signs of hypoglycemia were first adequately described by Mann and his collaborators. The low blood sugars were produced in dogs by removal of the liver. The description of this condition enabled the Toronto investigators to recognize that the effects of large doses of insulin were the same as those due to hypoglycemia produced by other means. The signs and symptoms vary in the different species. The first signs in the rabbit are hyperexcitability and desire for food. The excitability becomes greater, and mild and then severe convulsions are exhibited. The head is retracted and the hind limbs extended in the intervals between convulsive seizures. Coma is frequent. The animals may exhibit rigor mortis immediately after death. The signs in dogs are quite similar. Mice, in some instances, may become comatose without exhibiting convulsions. Cold blooded animals do not show any signs until

TABLE 55

Spontaneous hypoglycemia or dysinsulinism

<i>Hyperinsulinism:*</i> (Hyperactivity or tumor of islands of Langerhans)	<i>Interference with gluconeogenesis in liver</i>	<i>Hypofunction of anterior pituitary, adrenals or thyroid</i>
<i>In experimental animals:</i>	<i>In experimental animals:</i>	<i>In experimental animals:</i>
Hypertrophy after duct ligation?	Hepatectomy	Removal of pituitary (anterior lobe)
Hypertrophy after anterior pituitary extracts?	Interference with arterial blood flow	Removal of adrenals
No tumors carefully studied	Poisoning: Phosphorus Chloroform Hydrazine Synthalin, etc.	Removal of thyroid
	Deposition of fat	Hypoglycemia or (increased susceptibility to insulin)
<i>Clinical observations:</i>	<i>Clinical observations:</i>	<i>Clinical observations:</i>
Cases of hyperplasia and hypertrophy	Hepatitis	Hypoglycemia in so-called pituitary cachexia or Simmond's disease
Cases of tumor	Carcinomata	
	Yellow fever	
	Acute yellow atrophy	
	Poisoning: Phosphorus Carbon tetrachloride	Hypoglycemia in Addison's disease (some cases)
	Benzol	Increased susceptibility to insulin after thyroidectomy
	Chloroform	
	Synthalin, etc.	
	Surgical interference with blood flow	

There may also be excessive utilization of sugar by muscles—dogs in tread mill, marathon runners, etc.

* The term "hyperinsulinism" was introduced by Seale Harris in 1924 to describe cases exhibiting signs of hypoglycemia. The first report of a tumor of the islet cells which in this case had secondary growths in the liver was made by Wilder, Allan, Power and Robertson in 1927. Many cases of tumor have now been studied.

many hours or even days after insulin injections. The signs and symptoms in man have been ex-

tensively studied in the laboratory and clinic. The initial symptoms may be hunger or a feeling of nervousness—a sense of impending danger. A little later there may be profuse perspiration, alternate pallor and flushing of the face, vertigo and diplopia. The blood sugar at this stage is 0.06–0.04 per cent but the level varies greatly in different individuals. Most hypoglycemic reactions proceed no further than this. In very severe cases there may be delirium, convulsions, and death. The true blood sugar may decrease until only non-sugar-reducing power remains.

Sakel's insulin-shock treatment for schizophrenia has focussed attention on the metabolism of brain and the effects of prolonged hypoglycemia. Brain tissue utilizes carbohydrate almost exclusively. Hypoglycemia interferes with the supply and produces much the same condition as O₂ deficiency. The electrical activity of the cerebral cortex is depressed in hypoglycemia and restored to normal by the administration of glucose. The reduction in the oxidative metabolism of brain is undoubtedly responsible for this and other changes.

Cerebral damage, which may be permanent, has been observed in both animals and man as a result of prolonged hypoglycemia.

Alleviation of hypoglycemia

The intravenous administration of glucose is the most effective method of alleviating hypoglycemia. The prompt recovery of almost moribund animals provides one of physiology's most fascinating demonstrations. Mannose is almost as useful as glucose, and fructose also occupies a preferential position. Galactose and maltose have a slight but transient effect. Sucrose,⁶ lactose and pentoses are not effective. Glycogen and glycerol have been shown to exert some beneficial action. The effect of these substances in hypoglycemia is probably largely dependent on the rapidity with which they are transformed into glucose in the liver. Fructose may be converted slowly to glucose in muscle but there is a possibility that it may be burned directly (Griffiths and Waters). It is generally assumed that the only sugar directly oxidized in the muscle, where a large part of the total oxygen use takes place, is d-glucose. The usefulness of the other carbohydrates would therefore depend on the ease of their conversion into this sugar. Adrenaline and pituitrin may be used to alleviate hypoglycemia but glucose is much more

⁶ Carbohydrates which form glucose are, of course, effective. The above statement refers to the results of intravenous injections.

efficacious and safe. Liberation of adrenaline is, however, one of the physiological mechanisms by which hypoglycemia is corrected. Intense anger, such as that which might well be experienced by a diabetic whose hypoglycemia was mistaken for alcoholic intoxication (Duncan) may correct hypoglycemia through liberation of adrenaline.

THE INSULIN CONTENT OF THE PANCREAS UNDER DIFFERENT CONDITIONS

The insulin content of the pancreas has been determined in various animal species. The insulin is extracted from minced pancreases with an acid aqueous alcohol solution. Certain contaminating material is removed and the active material is precipitated. This is then redissolved and estimated by the mouse method of assay. In the dog the insulin content of the free splenic end of the pancreas is greatest, that of the attached duodenal portion has an intermediate value, while that of the free duodenal end is lowest, the values being about 4, 3, and 2 units per gram, respectively. In partially depancreatized dogs, provided sufficient pancreas is left to prevent the onset of diabetes, the insulin content does not differ from that of the corresponding part in a normal dog, nor are any degenerative changes in the β cells noted. If diabetes supervenes, hydropic degeneration of these cells is observed, and the insulin content of the remnant of pancreas falls to extremely low values. The daily injection into dogs of diabetogenic extracts from the anterior lobe of the pituitary gland produces a prompt and profound decrease in the insulin content of the pancreas (in seven days to 0.2 units per gram). If the injections are stopped at this stage, the insulin content is restored to normal within four days. If the administration is continued the insulin is reduced to negligible amounts. No recovery will occur when this point is reached. Simultaneous administration of insulin prevents or greatly modifies the fall in the insulin stores. This fact strongly suggests that the β cells are permanently damaged by the extract through overwork and that the simultaneous administration of insulin relieves the cells of some of this excessive demand for the hormone.

Starvation (seven days) or a diet rich in fat produces a decrease in the insulin content of the rat's pancreas to about half the normal value, which is about 24 units per rat. These animals have their insulin stores speedily restored to normal (in six days) when they are returned to a

balanced diet; carbohydrate alone effects a partial restoration. Daily injection of insulin into rat causes an even more marked decrease in the insulin content of the pancreas than does starvation (Haist and Best). Massive doses of insulin over prolonged periods may produce atrophic change in the pancreatic islets of partially depancreatized dogs which survive the treatment (Mirsky).

The injection of anterior pituitary extracts in certain strains of rats increases the islet volume and the insulin content of pancreas (Young Richardson and Marks). The effect of various hormones of the anterior pituitary on the insulin content of rat pancreas has been studied by Fraenkel-Conrat, Herring, Simpson and Evans. The purified lactogenic substance increased the insulin content in both normal and hypophysectomized rats. Growth hormone decreased the insulin content in normal and adrenalectomized animals but the effect could not be demonstrated after removal of the pituitary. Neither removal of the pituitary, the adrenals, nor the administration of cortical extracts changed the insulin content of the pancreas in the intact rat (Haist and Bell). It would appear probable, however, that cortical sterols which produce diabetes in normal animals will be found to lower the insulin content.

Subcutaneous estrogen transplants or the administration of stilbesterol produce an increase in the insulin content of rat's pancreas. This effect is not observed in the absence of the pituitary (Griffiths, Marks and Young; Funk). Stilbesterol may exert a diabetogenic effect in force-fed normal and partially depancreatized rats (Ingle).

The effect of age on the insulin content of the pancreas has been studied in the cow. In fetal calves under 5 months the concentration was 34 units per gram; in calves 6 to 8 weeks old, 10 units per gram; in heifers 2 years old, 5 units per gram; in cows over 9 years, 2 units per gram. Pregnant cows 7 years old and older showed no change from the normal insulin content of about 2 units per gram (Scott and Fisher). In Wistar rats the total insulin content of the pancreas increases with age.

Pancreases obtained from non-diabetic persons at autopsy have an average insulin content of about 2 units per gram. This is probably somewhat lower than the true value. Pancreatic tissue from diabetic persons shows wide variation, the average content of those studied being 0.4 units per gram.⁷ The insulin content of a tumor of islet tissue surgically removed from a patient suffering

⁷ These studies present great difficulties and much further work is needed to provide reliable data.

from hyperinsulinism may be as high as 214 units per gram.

It is, of course, apparent that these "insulin contents" indicate the balance between the rate of production of the hormone in the islets and the rate of liberation. There is good reason to believe that under certain conditions the rate of liberation is proportional to the content. Under other circumstances this may not be true. The conclusion has been drawn from some of these results that the islet cells are "rested" after administration of insulin, by starvation and by a high fat diet and that less insulin is excreted by the pancreas than under normal conditions. Partial pancreatectomy, sufficiently extensive to result in diabetes, or administration of diabetogenic extracts causes (1) marked stimulation of the islets and (2) subsequently degenerative changes and loss of insulin.⁸

THE USE OF INSULIN IN NON-DIABETIC CONDITIONS

Favorable results have been claimed for the use of insulin in a very great variety of non-diabetic conditions. It has been used in pernicious anemia, in acute infectious diseases, in eclampsia, in pernicious vomiting of pregnancy, and in hepatitis—to mention only a few. While it is conceivable that insulin might be of slight benefit in some of these conditions, it would appear that equally satisfactory results can be secured by the administration of glucose alone. It is a clinical fact that the administration of glucose produces favorable results in a variety of hepatic abnormalities. A high glycogen content protects the liver cells from damage and the inhibition of gluconeogenesis produced by both insulin and glucose may also play a role.

Insulin can now be considered, however, an established adjuvant in the treatment of certain cases in which lack of appetite prevents the ingestion of adequate amounts of food. The physiological basis for this use of insulin in these non-diabetic individuals rests very largely upon the increase in hunger and appetite which may be caused by the administration of sufficient material to produce a definite but not too marked hypoglycemia. In 1924 Bulatao and Carlson reported that production of hypoglycemia in experimental animals by the subcutaneous injection of insulin was uniformly accompanied by hypertonus and hypermotility of the stomach. The gastric tonic-ity and motility increase as the hypoglycemia deepens until complete tetanus is reached, which

persists until the dog exhibits hypoglycemic convulsions or until sugar is given. The effect of sugar is immediate, but if a large dose of insulin has been given the hyperactivity of the stomach returns as soon as the blood sugar falls again. The first record of the increase in gastric peristalsis in the human individual after insulin administration was that of Dickson and Wilson, 1924. An hour and ten minutes after the administration of insulin the tone, depth and rate of peristalsis and rate of emptying of the stomach were definitely increased. This condition persisted for two hours, when the blood sugar was found to be 70 mgm. per 100 cc. Glucose was then given, and while the acute symptoms were definitely relieved the hunger persisted. Subsequently Quigley, Johnson and Solomon studied the effect of insulin on the gastric movements of four human subjects. They found that doses of from 12 to 20 units of insulin definitely increased the gastric activity. The first definite augmentation was observed about an hour after the injection and persisted for at least five hours. There was prolonged duration of the hunger period, and this was considered to be the most characteristic effect of insulin. The increased peristalsis produced by insulin is not inhibited by such procedures as smoking, unpleasant emotions, body discomfort, or the presence of moderate amounts of non-carbohydrate food in the stomach. The increased movement was inhibited by atropine. The immediate relief of the excess peristalsis and hunger when appropriate amounts of glucose were given was confirmed.

It is known that insulin does not exert its effect on gastric motility and secretion after section of the vagus nerves. This means that either insulin acts centrally by stimulating the vagus, or that the continued elaboration of acetylcholine, which we now know is an essential part of the mechanism by which the vagus exerts its action, provides a foundation upon which the peripheral effects of insulin may be superimposed.

Insulin augments also, to some extent, peristaltic movement in the duodenum and in the colon, but the effect is not as marked as in the case of the stomach. It will be remembered that one of the early symptoms observed in experimental animals and also in human subjects after the administration of insulin is an increase in hunger. In animals an attempt to consume material of little nutritive value which under ordinary conditions they would not attempt to eat is often observed. It would appear, therefore, that the clinician is able to take advantage of this situation by providing nutritious food for his hungry patient. The increase in weight observed in both animals and patients when appropriate doses of insulin are given for prolonged periods is due

⁸ For references to work on insulin content of pancreas, see Haist, 1944.

to increased deposition of fat, and possibly also to a slight extent by increased deposition of carbohydrate. The increase in weight is not attributable to any appreciable extent to the retention of water.

INFLUENCE OF OTHER ENDOCRINE GLANDS ON CARBOHYDRATE METABOLISM

The adrenals

The glucosuria produced by adrenaline was first noted by Blum. The intravenous route of administration gives the greatest rise of blood sugar but subcutaneous, intramuscular or intraperitoneal injections are effective. The immediate rise in the sugar of the blood is due to breakdown of liver glycogen to glucose. There may be a considerable decrease in the amount of liver glycogen. Adrenaline also mobilizes muscle glycogen (Cori) but here the immediate product is lactic acid and not glucose. A part of the lactic acid is carried by the blood to the liver where it is converted to glycogen, which in turn furnishes the blood with glucose. Muscle glycogen is therefore available indirectly to replenish blood glucose. When lactic acid from the muscles has been changed in appreciable amounts to glycogen in the liver the amount of substance in this organ may be increased over the normal level. Adrenaline therefore in moderate dosage, first causes a decrease and then an increase in liver glycogen. Very large doses over prolonged periods may lower both muscle and liver glycogen. The nervous control of adrenaline secretion has been discussed on page 689, and the manner in which thoracic autonomic impulses may affect blood sugar through its liberation will be appreciated. Adrenaline does not accelerate sugar formation from other substances in the liver. Diabetes has not been produced by the continued administration of adrenaline.

Insulin and adrenaline are not chemical antagonists but possess opposing physiological actions. Adrenaline accelerates the breakdown of both liver and muscle glycogen but the lactic acid made from muscle glycogen may result in an actual increase in the liver. Insulin promotes the formation of glycogen in both organs but the increase in muscle glycogen may be at the expense of sugar which would have formed liver glycogen. These are excellent examples of the manner in which the action of a hormone may be obscured by other effects. When the blood sugar is lowered to about 0.06 per cent by insulin an increased rate of liberation of adrenaline may be detected (Cannon; Houssay). Adrenaline has also been reported to

increase the rate of liberation of insulin from the pancreas.

There are several investigations the results of which have been interpreted to mean that adrenaline inhibits carbohydrate oxidation in the muscle. The evidence, fall in R.Q. when adrenaline is added to an intravenous injection of glucose, might also indicate an increased formation of sugar from fat. Adrenaline has not been shown to depress carbohydrate oxidation in the liverless preparation.

THE ADRENAL CORTEX AND CARBOHYDRATE METABOLISM. After double adrenalectomy in some species (cat and rat) the carbohydrate reserves of the liver and muscles are depleted and there may be definite hypoglycemia (Britton and Silvette). These workers showed that the hypoglycemic condition may be corrected when the cortical hormone and glucose are provided but not when the latter alone is given. They reported that the administration of extracts of the cortex elevated the carbohydrate stores of adrenalectomized animals well beyond the normal limits. Insulin and glucose do not increase glycogen deposition in the adrenalectomized animal unless cortical extract is supplied (Britton) but it is possible that this effect might occur if the animals were supplied with a diet adequately low in potassium and high in sodium. Long and his collaborators have extended the earlier experiments of Britton and Silvette and find rather remarkable increases in liver glycogen in fasted or fed normal animals when extracts of the adrenal cortex were administered. Muscle glycogen was not affected by the cortical material in these experiments but may be increased when adequate amounts of sugar are supplied. Corticosterone and dehydrocorticosterone had the same effect as cortical extract.

After Houssay's demonstration that removal of the pituitary gland attenuates the severe diabetes resulting from total pancreatectomy in the toad and dog, Hartman and Brownell, and Long and Lukens, showed that a very similar change could be produced by adrenalectomy in the depancreatized cat or dog. It has been shown by Lukens and Dohan that the diabetes of adrenalectomized depancreatized animals and also that of hypophysectomized depancreatized animals can be increased in severity by the injection of cortical extracts.

Long, Katzin and Fry have shown that the rat, partially depancreatized by the method of Shapiro and Pincus, is an excellent preparation for the demonstration of the role of the adrenal cortex in

carbohydrate metabolism. Adrenalectomy attenuates the diabetes which may be observed in these animals. The grafting of cortical tissue may restore the glucosuria to the extent which has been observed before adrenalectomy.

The relative potency of various adrenal steroids has been studied by Long and his collaborators, by Kendall and by Ingle and Thorn. The carbohydrate levels of the body are restored and the glucosuria of partially depancreatized or adrenalectomized partially depancreatized animals is augmented to the greatest extent by corticosterone and its derivative with an hydroxyl or ketone group at C₁₁. Cortin has a somewhat favorable effect on carbohydrate storage but 11-desoxycorticosterone has very little action in the dosage which is effective in the maintenance of life and mineral balance in adrenalectomized animals. In much larger amounts it may exert some favorable influence. The injection of 5 milligrams a day of 11-dehydro-17-hydroxycorticosterone is followed by glucosuria, ketonuria and an increased excretion of nitrogen, phosphorus and potassium in partially depancreatized rats. Ingle has recently reported that the dehydro compound in doses of 10 milligrams a day may produce hyperglycemia and glucosuria in normal rats. It is established, therefore, that these adrenal compounds may be very powerful diabetogenic agents.

It has been shown by Long and his collaborators and by Ingle and other workers that the mechanism through which these adrenal extracts produce glucosuria is by stimulating gluconeogenesis from protein but as the increase in nitrogen excretion is insufficient to account for the extent of the glucosuria, interference with glucose oxidation has also been postulated.

Some but not all of the abnormalities of carbohydrate metabolism in adrenalectomized animals are apparently due to the disturbance in sodium and potassium metabolism. Thus the delayed absorption of sugar and fat and the failure to store glycogen from glucose can be favorably affected by appropriate salt treatment. On the other hand the sharp fall in carbohydrate levels in fasting adrenalectomized animals and the amelioration of diabetes in partially depancreatized rats by adrenalectomy are not corrected by feeding sodium salt but are by the administration of suitable cortical material.

The question arises as to how much of the diabetogenic action of the anterior pituitary gland is exerted through the adrenal cortex. The evidence on this point is somewhat conflicting. It would

appear that the pituitary preparation may exert some diabetogenic action in the absence of the adrenal. The presence of some cortical hormone is, however, necessary for the action of the pituitary factor which acts independently of the adrenal. A part of the pituitary effect is undoubtedly exerted through the adrenal cortex.

Many of these findings which have been obtained on experimental animals, have been confirmed by Thorn and his colleagues in studies on patients with Addison's disease.

The pituitary and carbohydrate metabolism

It has been appreciated for many years that abnormalities in carbohydrate metabolism may be associated with acromegaly of long standing or with the presence of various pituitary tumors. In 1908 Borchardt found that an extract of the posterior pituitary raised the blood sugar. In 1911 Cushing observed that "pituitary deficiency" may be accompanied by an increased carbohydrate tolerance. When insulin became available Burn demonstrated an antagonism between "puititrin" and insulin, and several workers (Olmsted; Geiling; Houssay) showed that animals were more sensitive to insulin after removal of the pituitary body.

It appeared for a time that both the oxytocic and pressor principles of the posterior lobe produced hyperglycemia and thus interfered with the action of insulin. The work of Ellsworth and others indicates that the oxytocin is probably the more important factor from this viewpoint but it is doubtful, from the dosage necessary to produce the effect, whether this is of physiological significance. Griffiths has reported that posterior lobe extract, i.e., the vasoconstrictor principle, interferes with the absorption of insulin. The action of subcutaneously administered insulin is inhibited but when the intravenous route is used this effect is not observed.

In recent years interest has been focussed on the anterior lobe of the pituitary by the brilliant researches of Houssay and his collaborators and of other investigators. The main points established in Houssay's laboratory are as follows: (a) Removal of the anterior lobe of the pituitary increases the sensitivity to insulin of the normal animal and diminishes the intensity of diabetes in the depancreatized animal. (b) Injections of preparations from the anterior pituitary into normal or hypophysectomized animals diminish their sensitivity to insulin and increase the severity of the diabetic state in hypophysectomized-depancreatized (Houssay) animals. (c) The administration of a suitable

extract of the anterior pituitary can induce a diabetic condition. This point was independently established by the reports of Evans and his colleagues and of Baumann and Marine, which preceded that of Houssay.

The effects of pancreatectomy and hypophysectomy are contrasted in the following summary, and the condition of the animal from which the pancreas and the pituitary have both been removed is briefly described.

<i>Pancreatectomy (Dog)</i>	<i>Hypophysectomy (Dog)</i>
Hyperglycemia	Low blood sugar, hypoglycemic convulsions during fasting
Polyuria	
Glycosuria	
Ketonuria	
Azoturia	
Insulin necessary for survival	Greatly increased sensitivity to insulin
Metabolic rate normal or slightly raised	Low metabolic rate
Decreased ability to utilize carbohydrate	Carbohydrate furnishes increased proportion of fuel
Decreased ability to form glycogen	Rapid disappearance of liver and muscle glycogen due to utilization of carbohydrate and decreased gluconeogenesis. ⁹
Increased gluconeogenesis	

Pancreatectomy and hypophysectomy

Animals survive without insulin. Polyuria, glucosuria, ketonuria, azoturia slight or absent. Administered carbohydrate partially or completely retained, i.e. carbohydrate utilization much better than in depancreatized dog. Metabolic rate low. Glycogen deposition.

PERMANENT DIABETES. The anterior pituitary gland contains a number of substances which affect carbohydrate metabolism in a variety of ways. These will now be considered briefly. Evans, Meyer, Simpson and Reichert in 1932 demonstrated the production of a prolonged diabetes in normal intact animals by anterior pituitary extract. F. G. Young, 1938, was however, the first to produce a permanent diabetes comparable in intensity to that resulting from complete pancreatectomy, by injection of extracts of the anterior lobe of the pituitary. He has found, in a very large number of dogs, that he is able consistently to produce a permanent state of diabetes by the daily injection, either intraperitoneally or subcutaneously, of a preparation of anterior lobe material. The per-

manent state of diabetes may be produced after as few as eleven daily injections but more are usually required. The diabetogenic activity, that is, the active material which will produce permanent diabetes in dogs, is associated with the globulin and pseudoglobulin fraction of the pituitary extract. The active principle is not available as yet in a pure state and it is notable that it possesses very distinct growth-promoting activity. Young's work has been confirmed by Campbell and Best and by Dohan and Lukens and many others. Degenerative lesions of the islet cells of the pancreas were first noted in these permanently diabetic animals by Richardson and Young. Signs of proliferative changes in the islet cells in the early stages of the injections were found by these workers and by Ham and Haist who also observed proliferative changes in the acinar and duct cells of the pancreas. The diabetogenic extract produced proliferative changes in various other glandular tissues in the body. Campbell and Best noted that the diabetic state produced by the pituitary extract was not intensified by complete removal of the pancreas and secondly, that the insulin content of pancreas was reduced to a negligible quantity. This latter point has been discussed elsewhere.

It would appear that the main effect of the substance or substances which produced the permanent diabetes is exerted upon the Islands of Langerhans. These cells are apparently first stimulated and then destroyed by the repeated injections of the active material.

The permanent diabetes produced by the above procedures differs from that caused by pancreatectomy, in that the animals may live for long periods without the administration of insulin. In some cases, however, insulin is required. Starvation or a diet very rich in fat causes a marked diminution in the intensity of diabetes in the permanently diabetic animal. The prolonged administration of crude diabetogenic preparations may produce a refractory state which is due to the appearance of an antistubstance (Lukens and Dohan) but it is unlikely that this will appear when a highly purified substance is used.

The production of permanent diabetes by the diabetogenic substance of the anterior pituitary, can be prevented by the simultaneous administration of large doses of insulin (Haist, Campbell and Best). The islet cells are protected from profound degenerative changes, the insulin content of the pancreas remains at a moderately high level, and the state of permanent diabetes is not induced.

⁹ For direct evidence of this effect see Crandall and Cherry.

Lukens and Dohan have shown that permanent diabetes produced in partially depancreatized cats by administration of the diabetogenic substance of the anterior pituitary gland, can be cured by the use of insulin, by a reduction in the caloric value of the diet or by an increase in its fat content. Recovery from early diabetes has followed a reduction in the diet only when the diabetes was very mild but treatment with insulin produced recovery at this stage regardless of the severity of the disease. If treatment were delayed until after the Islets of Langerhans had become atrophic, no recovery was possible.

It is to be noted that in the prevention and cure of this experimental diabetes, the level of the blood sugar is probably the most important factor which determines the direction in which the islet lesions will progress. This interpretation is supported by all the results which Young; Haist, Campbell and Best; and Lukens and Dohan have obtained and is in line with the earlier studies of F. M. Allen, Copp and Barclay and others.

THE GLYCOTROPIC OR ANTI-INSULIN ACTION OF ANTERIOR LOBE EXTRACTS. It was first demonstrated by Houssay and Potick and adequately confirmed by many later investigators that treatment with anterior lobe extract can induce in either normal or hypophysectomized animals an insensitivity to the action of insulin.

Bennett observed hyperglycemia and increased liver glycogen values upon prolonged administration of the adrenotropic hormone. Jensen and Grattan, and Ingle have shown that the adrenotropic substance as well as extracts of the adrenal cortex, and crystalline corticosterone produce a definite glycotropic effect. The adrenocorticotrophic factor failed to produce this anti-insulin effect or to promote deposition of liver glycogen in adrenalectomized mice. These findings, therefore, strongly suggest that the glycotropic effect of anterior pituitary extracts is due to the adrenocorticotrophic factor and that the anti-insulin action is due to the storage of large amounts of glycogen in the liver. This glycogen is presumably available to counteract the hypoglycemic effect of insulin.

THE GLYCOSTATIC EFFECTS OF ANTERIOR PITUITARY EXTRACTS. It is well established that hypophysectomized animals are unable to preserve their glycogen stores as normal animals do during fasting. It has been found by Russell and Bennett that this function can be restored, under certain conditions, by anterior pituitary extracts. In subsequent experiments it has been shown that this

action is not through the adrenal since muscle glycogen can be maintained at a normal level in the absence of both adrenal glands. The existence of a separate glycostatic factor has been postulated since the action is not associated with any of the established anterior lobe substances and a unit of glycostatic activity has been suggested in terms of the minimal dose necessary to maintain normal muscle glycogen in hypophysectomized animals. Russell's finding that, although this action is not exerted through the adrenals, it is greatly increased by the presence of cortin, may lead to very important developments.

THE PANCREOTROPIC ACTION OF ANTERIOR PITUITARY EXTRACTS. In 1933 Anselmino, Herold and Hoffmann reported that frequent injections of anterior lobe extracts in rats produce in a few days an increase in the size and number of the Islets of Langerhans. Richardson and Young were not able to confirm the findings under the conditions defined by the German investigators. They were, however, able to show that the daily treatment of rats with crude anterior pituitary lobe extract for a period of two weeks doubled the amount of islet tissue in the pancreas. More recently Marks and Young showed that the insulin content of rat pancreas was greatly increased under these conditions. (See Insulin Content of Pancreas.)

Mirsky and Swadesh have suggested that the influence of the pituitary gland on growth may be dependent on its pancreotropic function.

It will thus be apparent that the effect of the anterior pituitary gland on carbohydrate metabolism is exerted through a variety of mechanisms. The diabetogenic action which is in large part due to destruction of the Islets of Langerhans, produces its effect by eliminating the antidiabetic hormone, insulin. The action of this substance can therefore be described by enumerating those changes which are due to the absence of insulin from the body. The glycotropic or anti-insulin substance exerts its effect through the adrenal cortex. This action is primarily on the deposition of glycogen in the liver. The action of anterior pituitary hormones in the production of diabetes is more extensive than this. The work of Long and his collaborators has shown that diabetes may be produced in the partly depancreatized rat by administration of these substances but the extent to which the diabetogenic substance of the anterior pituitary affects the pancreas through the adrenal cortex, has not as yet been established. The glycostatic substance by immobilizing glycogen in the muscles may also contribute to the diabetic effect. Sup-

pression of carbohydrate oxidation by anterior lobe extracts has also been postulated but it is difficult to separate this effect from diminished gluconeogenesis in the intact animal. Direct evidence in favor of this suppression is, however, accumulating.

The anterior pituitary glands also affect carbohydrate metabolism through the thyrotropic and perhaps also through the gonadotropic substances. Removal of the adrenal cortex, thyroid, or the gonads produces histological changes in the anterior pituitary but the functional significance of these is not as yet clear.

Inhibition of the anterior pituitary effect on carbohydrate metabolism by the use of X-rays or by injection of estrogenic substances can be demonstrated in animals and in man but little of practical clinical value can be expected from these procedures.

The thyroid and carbohydrate metabolism

The aggravation of diabetes in man by hyperthyroidism and its amelioration by removal of the thyroid establishes a link between this gland and carbohydrate metabolism. It is surprising that very little influence on the diabetes of depancreatized animals can be demonstrated by thyroidectomy. This may be due in part to incomplete removal of thyroid tissue. When very extensive atrophy of the thyroid is produced by hypophysectomy in dogs, the blood sugar and a normal level of urinary nitrogen can be maintained for long periods during fasting if thyroxin is supplied. Without it hypoglycemia may soon terminate the experiment. Thus it appears that the thyroid may play a role in the effect of the anterior pituitary on carbohydrate metabolism. The slight effect of thyroxin administration on the intensity of pancreatic diabetes in animals still requires explanation.

The administration of thyroid substance or of thyroxin has no immediate effect on blood sugar but a loss of liver glycogen may be demonstrated within six hours. There is also apparently a rise in the protein content of liver pituitary perhaps to mobilization from peripheral tissues. Increased gluconeogenesis from protein can be readily demonstrated when thyroid substance is fed. An increase in the d-amino-acid oxidase activity of liver has been reported.

In clinical hyperthyroidism a mild hyperglycemia and glucosuria may be present. A comparable condition may be produced in animals by administration of thyroid material. At this stage liver glycogen is easily mobilizable (the actual amount present may be less than normal) and

adrenaline elicits more hyperglycemia and insulin less hypoglycemia than normally.

When thyroid feeding is continued there is profound decrease in liver, muscle and heart glycogen. In this second stage the animals are resistant to adrenaline and extremely susceptible to insulin. They may exhibit spontaneous hypoglycemia and develop it as a secondary result of a small injection of dextrose. This latter effect may be due to the liberation of insulin the action of which is not buffered by liver glycogen.

Thus the effect of the thyroid on carbohydrate metabolism is the resultant of two actions (1) increased oxidation of carbohydrate in tissue generally, and (2) the increased rate of hepatic gluconeogenesis.

THE NERVOUS REGULATION OF CARBOHYDRATE METABOLISM

As is the case with many other aspects of carbohydrate metabolism Claude Bernard paved the way for the investigation of the influence of the nervous system. Bernard (1855) punctured the floor of the fourth ventricle in unanesthetized animals and observed that the piqure produced a prolonged glucosuria. (The blood sugar of a rabbit may rise to 0.40 per cent within an hour and the effect may persist for several days or longer.)

It has been appreciated for some time that lesions in the hypothalamic region may cause glucosuria and the relation of these lesions to pituitary secretion has been in doubt. While lesions in this region might interfere with the absorption of the pituitary hormones or more likely, stimulate or destroy the nerve fibers going to the gland, it has been established that stimulation of the thoracic autonomic center in the hypothalamus may produce hyperglycemia. This gave rise to the idea that lesions lower in the brain stem might act by irritating the fiber tracts from the thoracic autonomic center but the situation is apparently not so simple. Donhoff and Macleod attribute special significance to the pons and there may be various centers, the impulses from which affect the level of blood sugar by more or less indirect paths.

There appears to be no doubt that Bernard's puncture damaged the cerebellum and also involved the pons. The nerve tracts affected are not accurately known but Donhoff and Macleod find that injury to the pons or the medulla immediately adjacent is essential for the development of hyperglycemia following decerebration. It ap-

appears probable that irritation setting up nerve impulses is responsible for the hyperglycemia rather than the interruption of nerve pathways. Decerebration above the pons does not produce hyperglycemia. The mechanism of action of the nerve impulses set up by the piqure is not entirely settled but several investigators find little response after removal of the suprarenals. The fact, however, that stimulation of the nerves in the hepatic plexus after removal of the suprarenals or of the nerves in the cut hepatic pedicle produces hyperglycemia by breakdown of liver glycogen, provides a mechanism for the more direct action. It appears probable as Macleod and Pearce suggested that while nerve impulses passing directly to the liver produce glycogenolysis, the presence of the adrenals may be necessary to maintain the integrity of the glycogenic nerve fibers. Glycogenic impulses are apparently conveyed by both the thoracic autonomic and the parasympathetic systems but the former are usually the more effective. This is particularly marked when animals with good supplies of liver glycogen are studied.

It will be appreciated that lesions of the brain involving (1) the pathways which carry glycogenolytic impulses to the liver or (2) the tracts which supply the adrenals, pancreas or pituitary may cause serious disturbances of carbohydrate metabolism. The first report of the production of such changes following lesions in the hypothalamus was made by Aschner in 1912. In recent years the subject has been studied by Keller and by Ingram and their collaborators. Stimulation of the posterior hypothalamic nuclei produces a hyperglycemia through the sympathico-adrenaline mechanism. Lesions of the paraventricular nuclei cause increased sensitivity to insulin and a prolonged hypoglycemia. Lesions of the tuber cinereum in the lateral hypothalamic area act in the same way as hypophysectomy in ameliorating the diabetes produced by pancreatectomy.

GLUCOSE TOLERANCE CURVES

When glucose is administered by mouth to a normal animal the blood sugar begins to rise within two or three minutes. This indicates that the sugar solution passes rapidly through the stomach to the duodenum. If large amounts of sugar are provided there may be considerable loss in the urine, i.e., *alimentary hyperglycemia* and *glucosuria*. After the usual meal, however, the hyperglycemia is not sufficient to produce glucosuria. When moderate amounts of sugar are given the rise in blood sugar is transient and the

return to the normal level rapid. This phenomenon is extensively used to test carbohydrate tolerance. The factors which determine the shape of the curve when from 50 to 100 grams of sugar are given by mouth are: (1) The rapidity of absorption, (2) the extent of the storage and utilization of glucose by the tissues, and (3) the rate of discharge of sugar from the liver. The first factor may, of course, be eliminated by injecting the sugar intravenously.¹⁰ The reaction of the tissues and of the liver to injected sugar may be direct or indirect. When more sugar is presented to the tissues more is utilized even though the insulin available remains constant. When the blood sugar rises the liver may discharge less sugar (Soskin, Allweiss and Cohn). The hyperglycemia may affect the liver and other tissues indirectly by increasing the insulin output and perhaps by other endocrine adjustments. The insulin liberated increases the oxidation and storage of glucose and decreases gluconeogenesis. An abnormal curve may indicate inability of the liver or pancreas, or of both to perform their normal functions. It might be due in part or completely to defective oxidation and storage in the muscles. It must be emphasized that an abnormal glucose tolerance curve *does not* necessarily indicate a deficiency of available insulin.

Undernutrition and carbohydrate metabolism

In 1873 Lehmann and in 1877 Claude Bernard noted a glucosuria in fasting animals after the administration of carbohydrate, and in 1890, Hofmeister, who made the first quantitative studies, named the condition "hunger diabetes". Utilization of carbohydrates is at a maximum in animals which have been fed on diets rich in these substances. After periods of fasting or of fat feeding, there is a definite impairment of glucose utilization which may easily be detected by the results of a glucose tolerance test. The feeding of an exclusively fat diet produces effects on glucose utilization indistinguishable from those of complete starvation. Proteins exert an effect intermediate between that of sugar and fat, i.e., some impairment of glucose utilization is produced by an exclusively protein diet. Diets adequate in other respects but providing a low caloric intake cause little disturbance in carbohydrate utilization. The administration to animals or human subjects

¹⁰ Normal dogs may be given 0.85 gram of glucose per kilogram per hour for long periods (Woodyatt) without producing glucosuria. This is approximately the same value as the maximum rate at which glucose is absorbed from the intestinal tract.

exhibiting hunger diabetes of a diet containing glucose causes a prompt improvement in carbohydrate tolerance.

The mechanisms of production and alleviation of the defect in carbohydrate utilization produced by fasting are not as yet completely elucidated. It would appear from the recent findings of Chambers, Cori and others that oxidation of glucose in the tissues is interfered with to a much greater extent than is glycogen formation. It has been established that the administration of insulin effects a partial restoration of carbohydrate utilization (Cori and Cori; Dann and Chambers). This finding suggests that insulin liberation may be depressed in hunger diabetes. Himsworth feels that a change in sensitivity to insulin is involved rather than a diminution of pancreatic output. On the other hand, the recent observation by Haist, Ridout and Best shows that the insulin content of the pancreas of rats may be reduced to nearly half the normal value by starvation or by fat feeding. This finding in conjunction with others supports the view that insulin liberation may be decreased. The evidence, which has been well reviewed by Chambers, does not indicate that the complete explanation of hunger diabetes will be found in the abnormal response of any one organ or tissue.

GLYCOGEN DISEASE. A clinical condition characterized by the enlargement of one or more organs resulting from the accumulation of glycogen has recently attracted the attention of research workers. The disease usually bears the name of von Gierke who published an autopsy report on a case in 1929. Van Creveld, in the previous year, had concluded that the hepatomegaly which he observed in a young boy was probably due to excessive glycogen deposition. The glycogen deposits may be in the liver, kidney, heart or in other tissues. The disease is characterized by hypoglycemia and ketosis in the fasting condition, by an abnormal effect of adrenaline which causes only a slight rise in blood sugar and lactic acid but a large increase in ketosis, and by an increased sensitivity to insulin. The glucose tolerance test gives a prolonged hyperglycemia without glucosuria. The glycogen content of the blood is increased and van Creveld noted a resistance of this material to glycogenolysis, but Schönheimer found no

abnormal properties of glycogen isolated from the liver or kidneys. The glycogen in these tissues does not, however, disappear at a normal rate after removal from the body and an interference with the glycogenolysis process is therefore indicated. The new knowledge of the steps by which glycogen breakdown proceeds makes possible many new and potentially important studies.

It would appear probable, as van Creveld has suggested, that glycogen disease is a continuation in childhood of a fetal condition in so far as certain aspects of carbohydrate metabolism are concerned. There are large deposits of liver glycogen in the fetus and this material is resistant to the action of adrenaline. It is well established that in some species the fetal pancreas at or near term, contains very high concentrations of insulin. Hyperinsulinism may produce excessive deposits of glycogen in well-fed animals and ketosis under fasting conditions. It has been suggested that the secretion of the anterior pituitary gland makes liver glycogen more resistant to breakdown. There are therefore various physiological leads to be followed in the attempt to elucidate the etiology of glycogen disease.

ALLOXAN DIABETES. This new type of experimental diabetes was first produced by Dunn, Sheehan and McLetchie (1943) who showed that alloxan has a selective necrosing action on the Islands of Langerhans. In 1937 Jacobs had noted the effect of alloxan in rabbits—an initial hyperglycemia and a subsequent hypoglycemia. No histological studies were made and Jacobs postulated an insulin-like action of alloxan. It has now been shown that the hypoglycemia is due to the liberation of insulin from the damaged islets and the diabetic state is caused by a failure of these cells to produce insulin. The diabetic action of alloxan has been demonstrated in the rabbit, rat, cat, monkey and dog. An attempt has been made to destroy the islet cells in advanced cases of hyperinsulinism in man by the administration of alloxan. Lesions in the liver and kidney, less marked than those produced in the islets, are seen in some species after the injection of this chemical.

There is, as yet, no evidence that alloxan has any physiological significance. A substance resembling it was reported, many years ago, in the urine and intestinal mucus in certain pathological conditions in man. Alloxan provides a convenient means for producing pancreatic diabetes, particularly in small animals which can not readily be depancreatized, and will thus be a most useful tool in the study of the diabetic state.

CHAPTER LI

FAT METABOLISM

CLASSIFICATION OF THE FATS AND FATTY SUBSTANCES OCCURRING IN THE BODY

When a tissue is thoroughly extracted with ether and alcohol almost all of the fatty substances are removed.

The amount of fatty acids combined in the cerebrosides and phospholipids may be determined by taking advantage of the insolubility of these materials in acetone to which some magnesium chloride has been added. The fatty acids may then be liberated and estimated by one of a variety of procedures. An estimate of the amount of the phosphorus containing substances can be obtained by determining the phosphorus content of the extract and similarly with those containing carbohydrate by estimating the sugar. The fatty acids combined with cholesterol can be determined by estimating the amount of bound cholesterol. The free cholesterol is removed by precipitation with digitonin and estimated gravimetrically or by colorimetric means. In another sample of the extract the bound cholesterol is liberated by saponification as with sodium ethylate and the total cholesterol determined. The difference between the free and the total is the amount of cholesterol combined with fatty acid and this can be calculated from the known combining weight of fatty acids with cholesterol. The result is an estimate of the amount of cholesterol ester. The difference between the total fatty acid content and the sum of the amounts combined with carbohydrate, phosphoric acid, and cholesterol, gives us an estimate of the amount combined with glycerol. The fatty materials or lipids may therefore be classified as follows:

(1) *Fats*. Esters of fatty acids and glycerol.

(2) *Lipoids*.¹

(a) *Phospholipids*. (Phosphatides).

Fatty substances containing fatty acids, phosphoric acid and nitrogenous groups (lecithin, cephalin and sphingomyelin).

(b) *Cerebrosides*. (Glycolipids). Combinations of fatty acid, sugar and a nitrogenous substance (phrenosin, kersin, etc.).

(c) *Waxes*. Esters of fatty acids and certain alcohols (but *not* glycerol), (cholesterol esters, beeswax, etc.).

(3) *Sterols*. Hydrogenated phenanthrene derivatives (free cholesterol, ergosterol, etc.).

(4) *Hydrocarbons*. (Squalene, carotene, etc.).

The triglycerides

CHEMICAL STRUCTURE. In the members of the first group, the fats, one molecule of glycerol is combined with three of fatty acid: oleic acid $C_{18}H_{34}O_2$, stearic acid $C_{18}H_{36}O_2$, and palmitic acid $C_{16}H_{32}O_2$, are the three which account for the bulk of the fatty acids of the neutral fat fraction of body tissues. The latter two are saturated, while oleic acid has a double bond in the middle of its fatty acid chain. This renders it less stable and more easily oxidized. Oleic acid is liquid at low temperatures while stearic and palmitic are solid even at body temperature. It is now thought that the glycerides are usually mixed, i.e., they contain two or more different fatty acids in their molecule. Fatty acids more unsaturated than oleic (linoleic and arachidonic) are also found in the triglycerides.

The neutral fats obtained from animal tissues contain fatty acids which have an even number of carbon atoms. The characteristic fatty acids in the depôt fat vary with different animals. Hilditch and Lovern have shown that certain fatty acid mixtures are characteristic of marine animals, others of fresh water fish and others for land animals. The fat of the fish, for example, contains large quantities of higher unsaturated fatty acids C_{20} and C_{22} , but in the depôts of ox and pig these are almost absent.

DISTRIBUTION. Reserve fat is found in the so-called interstitial tissue of all organs with the exception of the brain. There may be very large masses of this material in subcutaneous tissue and in various other places such as in the omentum, the perirenal fat depôt and so on. (See table 56.)

The distribution of fat has been found to be independent of the type of diet which, however, controls the amount and in many species the character of the fat deposited.

PHYSIOLOGY. The main function of the glycerides is undoubtedly to provide a source of energy.

¹ The phospholipids, cerebrosides and waxes which resemble fats may be termed lipoids or fat-like substances. The sterols and hydrocarbons while associated with fats are chemically quite distinct.

Fat not only furnishes more energy per gram (9.3 calories) than carbohydrate and protein but it is the only food material stored in the dry state. The total fat content of a well-nourished animal may be between 10 and 12 per cent and under unusual conditions much higher. A very large proportion of the total energy store of the body is in the form of fat.

While animals grow normally when diets containing only very small amounts of fat are provided, several investigators have reported that growth is seriously retarded on a diet free of fat (McAmis, Anderson and Mendel). Palmitic, stearic and oleic acids are not essential but Burr and Burr have provided evidence that certain of the unsaturated fatty acids are necessary. Growth is favorably affected by linoleic, linolenic and arachidonic acids and the development of skin

no difference in saturation of the fat from the superficial subcutaneous region and that of deep and warmer parts of the body. These latter workers used animals which are not normally subjected to extremely low temperatures.

Recovery from the depôt fat of a particular dietary fatty acid, has been repeatedly demonstrated. This deposition is, however, limited to the higher fatty acids (above C₁₀). Those of lower molecular weight are apparently called upon first for the provision of energy but they may be built up into longer chains and stored. Thus low molecular weight fatty acids may affect body composition. Schoenheimer and Rittenberg have shown that a portion of stearic acid (labelled with deuterium) may be desaturated to oleic acid and another degraded to palmitic acid. Unsaturated bonds may be hydrogenated and palmitic acid, for example, may be converted to others of shorter or longer length of carbon chains. Interconversion of the fatty acids within the body is thus well established.

TABLE 56
Distribution of adipose tissue in the rat
(After Mendel)

	PROPORTION OF TOTAL FAT
	<i>per cent</i>
Subcutaneous.....	50
Genital.....	20
Perirenal.....	12
Mesenteric.....	10
Inter-muscular.....	5
Omental.....	3

lesions (similar to acrodynia) is prevented. These acids should be considered separately in dietary studies since there are definite differences in the magnitude of their effects on growth and on the skin lesions. There is an interesting interrelationship of the actions of the unsaturated fatty acids and those of pyridoxin, pantothenic acid and other accessory food factors.

In some species, of course, the layers of fat in the subcutaneous spaces serve as an insulating mechanism against extreme cold. Thus in cold climates the fat deposited just under the skin contains a relatively large amount of oleic acid. It is therefore more liquid than the material which is found in the less superficial subcutaneous reserves. Henriques and Hanson have pointed out the fact that since the temperature of the outermost subcutaneous fat is appreciably lower than that of the deeper parts, the body requires a more easily mobilizable type of fat at this place. In a somewhat similar investigation of fat in different parts of the body Anderson and Mendel could find

Conversion of carbohydrate and protein to fat

The formation of body fat from carbohydrate of the diet was established by the classical work of Liebig (1852) and Lawes and Gilbert (1853). The rate at which the fatty acids are formed has now been studied by the use of deuterium. Schoenheimer and his colleagues found that palmitic and stearic were made at the same rate but that the formation of the unsaturated acids was slower. The body is able to introduce one double bond but not two and the highly unsaturated fatty acids (such as linoleic and linolenic) are therefore not found in this "synthetic" fat.

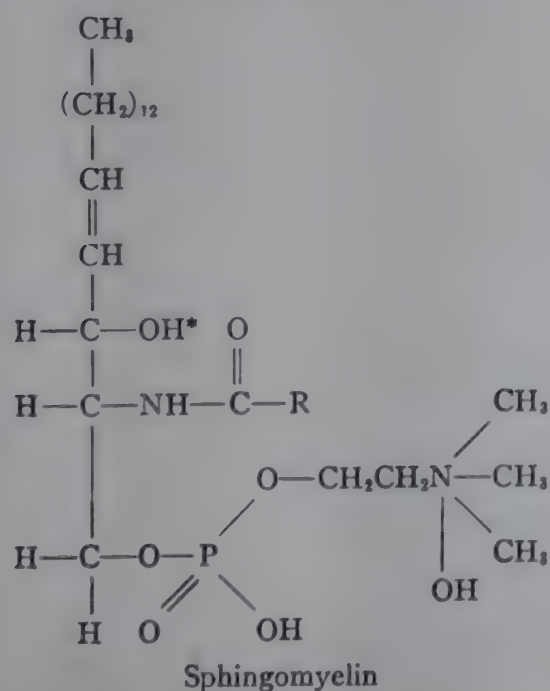
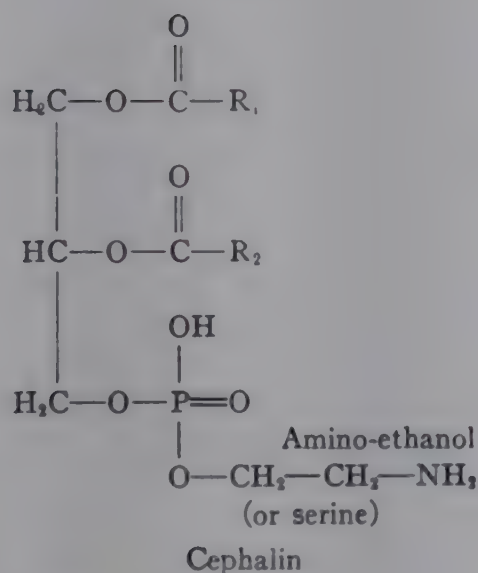
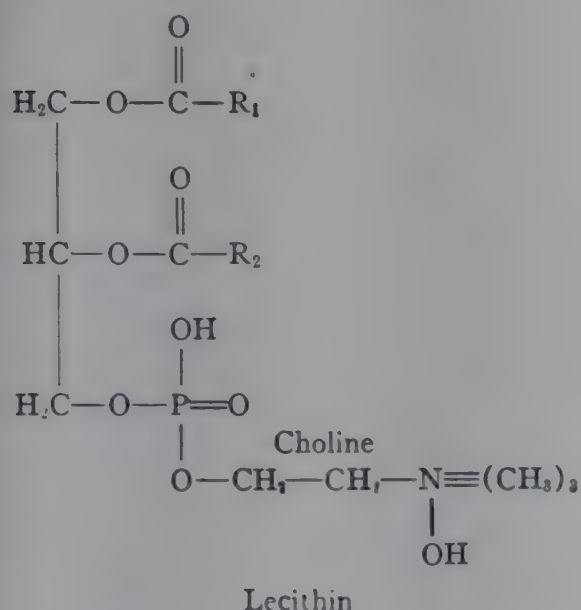
The formation of carbohydrate from protein is well established. It has been assumed that this newly formed carbohydrate is available for fat synthesis and good evidence for this assumption has been added recently by Longenecker and by Hoagland and Snider. On an almost exclusively protein diet the fat formed was similar in composition to that synthesized from dietary carbohydrate.

Many of these recent additions to our knowledge establish the fact that the fat depôts are not essentially inert storehouses of energy as was previously thought, but are centers of continuous metabolic activity.

The phospholipids

CHEMICAL STRUCTURE. The phospholipids may be divided into the monoamino-monophospho-

lipids in which the ratio of nitrogen to phosphorus is 1:1 and the diamino-monophospholipids in which the ratio of nitrogen to phosphorus is 2:1. The monoamino-monophospholipids are lecithin and cephalin and perhaps others that have not yet been identified.



* May be esterified with fatty acid.

The lecithins and cephalins are composed of glycerol and fatty acids as are the triglycerides, but one fatty acid may be considered to be replaced by the phosphoric acid-nitrogenous base complex. The base is choline in the case of lecithin and amino-ethanol in cephalin. Another cephalin has recently been isolated (Folch and Schneider) which contains the amino acid serine and this may provide another source of amino-ethanol. Folch and Woolley have found a cephalin fraction in *brain* and *spinal cord* which contains inositol. There is usually one saturated and one unsaturated fatty acid but in some cases two saturated or two unsaturated fatty acids may occur. Oleic and either palmitic or stearic acid are commonly found but more highly unsaturated fatty acids such as linoleic and linolenic have been identified. Sphingomyelin is a diamino-monophospholipid and contains two bases choline and sphingosine and one fatty acid radical but no glycerol is present. Different sphingomyelins containing respectively stearic, lignoceric and nervonic acids have been found.

DISTRIBUTION. The phospholipids, lecithin, cephalin and sphingomyelin are widely distributed in the body and it is thought that all cells contain one or more of these compounds. Sphingomyelin is present in much larger amounts in the brain and nerve tissues than elsewhere and is usually associated with the cerebrosides.

The cephalin content of the brain is considerably higher than the lecithin concentration. In the liver and spleen they occur in almost equal amounts while in the kidney, heart and lung, lecithin predominates in a proportion of about two to one. Cephalin and lecithin have been isolated from the gastric mucosa of pigs but sphingomyelin could not be demonstrated.

The evidence of the French workers Mayer and Schaeffer, and Terroine showed that the amount of phospholipid in a particular organ in a given species remains relatively constant under a variety of conditions including extreme starvation. As a result, they have called this fraction the "élément constant". While this evidence strongly suggests that the lipids are structural components of the cell there are many new findings which emphasize their rapid rate of turnover and their importance in metabolic processes. In table 57 the phospholipid content of various human tissues is given.

PHYSIOLOGY. As emphasized above the phospholipid content of the various tissues is much more constant than that of the neutral fat. How-

ever, this relative constancy must not be taken as evidence of phospholipid inactivity.

There are, however, significant variations in phospholipid due to the amount and character of the diet. The amount in muscle may decrease during fasting while that in the liver increases in some species. The body is able to synthesize the phospholipids if the constituents are available.

Various hormones affect the phospholipid values. Insulin decreases the plasma phospholipid. Repeated injections of thyroid substance increase the amount in liver while removal of the thyroid causes a decrease. With the onset of pregnancy in the human subject the plasma phospholipids show a rise which continues to term (the other

TABLE 57

*The lecithin, cephalin, and sphingomyelin content of normal human organs**

ORGAN	LECITHIN†	CEPHALIN‡	SPHINGOMYELIN‡
Brain†	4.81	20.42	5.00
Lung	3.85	2.00	1.45
Spleen	3.54	4.16	0.86
Kidney	3.10	3.26	0.72
Liver	4.81	4.62	0.38
Heart	4.47	2.06	0.34

* From Thannhauser et al. (J. Biol. Chem., **129**, 717, 1939).

† The values representing mg. per 100 mg. of dried organ.

‡ Including both white and grey matter.

lipids also increase). The work of Aten and Hevesy indicates that milk phospholipids are synthesized in the mammary gland.

Bloor has suggested that the phospholipid content of a tissue may be considered an index of the extent and variety of its physiological functions. Thus, the phospholipid content is increased with physiological activity and decreased when the cells become less active. A secreting salivary gland of the dog (Cambridge, Mayer and Valler) has a higher phospholipid content than the resting one on the other side. The development of the corpus luteum is accompanied by a very significant increase in its phospholipid content (Bloor, Okey and Corner). When the body temperature of rabbits and dogs was greatly reduced by immersion in very cold water, Mayer and Schaeffer found a decrease in the phospholipid content of the liver and a compensatory rise when the animal had recovered from the experience. The phospholipid content of rapidly growing malignant tumor cells

is higher than in normal tissue or in benign of the same tissue.

The relative constancy of the phospholipid content of most of the tissues, the antipathetic physico-chemical effects of cholesterol and phospholipids (Degkwitz) and the aversion of the phospholipids of certain tissues to be oxidized which the phospholipids of certain tissues and retain the highly unsaturated fatty acids support the view that these substances have functions other than to transport fat or to serve as intermediaries in fat metabolism in other ways. Sinclair has stressed the possibility that the phospholipids may act as agents for the transport of fatty acids within the cell. Oxygen may be taken up by the unsaturated bonds in their molecules and in different circumstances released again. If the greater solubility of the phospholipids in fluids, the high degree of unsaturation of the fatty acids (see p. 595) and the change in the level of the phospholipid content of blood as well as with the intensity of fat metabolism focus attention on their possible rôle as intermediaries. An interesting new chapter in the story of phospholipids has been built up around the physiological significance of choline, betaine, methionine, inositol as lipotropic factors. This will be discussed under "The Liver and Fat Metabolism" (p. 601).

The metabolic function of the phospholipids is most readily studied experimentally. The introduction of labelled atoms or groups into phospholipids so that the transportation and conversion into other substances can be followed in the organism has greatly increased the knowledge of the function of these substances. The use of active phosphorus P^{32} (Artom; Chalkoff; Sternum, introduced into fatty acids in place of hydrogen (Schoenheimer) and elaidic acid, the trans isomer of oleic acid which is indistinguishable from a natural fat but does not lose its label during metabolism (Sinclair) have been used in much of this work.

If, for example, the elaidic acid fed is converted into phospholipid as a preliminary step before combustion, then the fatty acid should appear in the phospholipids. If the phospholipids are involved as intermediaries in fatty acid metabolism they must undergo a rapid turnover, new molecules being synthesized to replace those lost by oxidation or diffusion.¹ Thus the rate of turnover

¹ Schoenheimer and Rittenberg (Proc. Roy. Soc. London, **1940**) have suggested the term "regeneration" place "turnover".

ity acids in the tissue phospholipids can be followed by the administration of labelled fatty acids. The turnover of the phosphoric acid is linked both to glycerol and the nitrogenous base measured by radioactive phosphorus.

By these methods it has been shown that the turnover of both the fatty acids and the phosphoric acid is most rapid in the mucosa of the intestine (during fat absorption) somewhat slower in the liver and much slower in the muscles and nerves. Several workers have determined rates of turnover of the lecithins, cephalins and sphingomyelins. Chargaff has stated that 24 hours after the administration of P^{32} more labelled phospholipid than cephalin is found in rat liver and intestine. Hevesy and Hahn found that in the liver the 4th hour the percentage turnover of the phospholipids is the same as that of the lecithins and sphingomyelins. By the 12th hour the percentage turnover of the phospholipids is the same as that of the lecithins and sphingomyelins. These latter investigators postulated the existence in tissues of two cephalins, one "fast" and the other with a "slow" turnover. The turnover of the sphingomyelins in liver is approximately the same as that of lecithin but in the brain the turnover is more rapid than either lecithins or cephalins.

In the brain the incorporation of P^{32} is a slow process and its loss from the brain occurs slowly. The turnover of the cephalins and sphingomyelins is slower than that of the lecithins. The rapid turnover of both the cephalins and lecithins in the liver suggests that they are intermediaries in fat metabolism.

The incorporation of administered P^{32} into plasma phospholipids is a much slower process in cor-

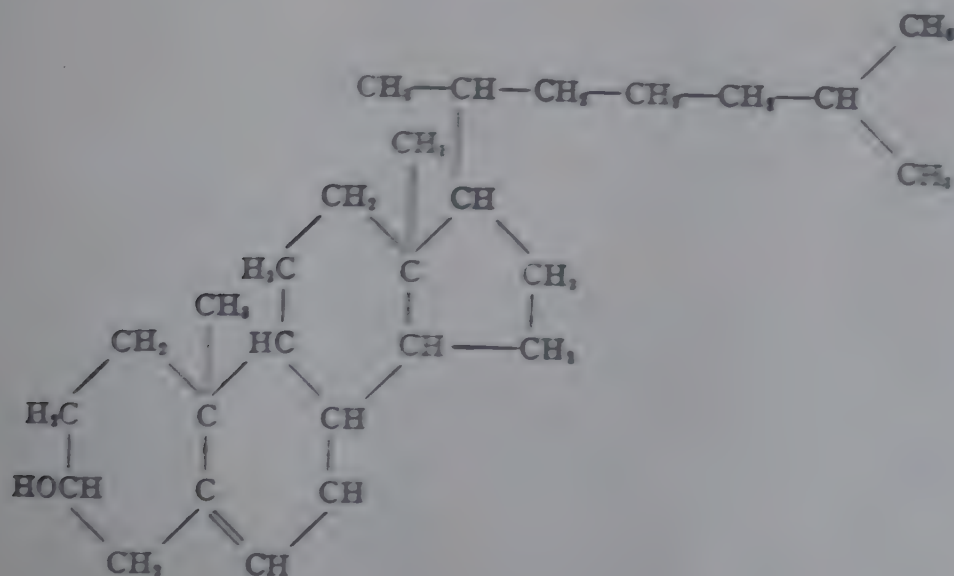
puscles than in plasma. In the hepatectomized dog 6 hours after the injection of P^{32} no radio-active phospholipid could be recovered in the plasma. This observation suggested that the liver is the main site (if not the only one) for phosphorylation of plasma phospholipids.

The cerebroside (glycolipids)

In the cerebroside the base sphingosine is combined with galactose or glucose and a fatty acid. Among these are phrenosin (cerebron) containing phrenosinic acid $C_{25}H_{49}O_6$ and keratin containing lignoceric acid $C_{24}H_{49}O_2$. Two other cerebroside have been reported—nervone which contains nervonic acid and hydroxynervone containing hydroxynervonic acid. The cerebroside, which differ from one another in the nature of the fatty acids or carbohydrate, can be distinguished from the phospholipids by the absence of the phosphoric acid group. They are found particularly in nervous tissue and only in minute amounts elsewhere in the normal body. Their physiological significance is unknown.

The sterols

CHEMICAL STRUCTURE. Cholesterol is the name applied to one of a group of sterols which are found in animal tissues. There are several sterols which differ from each other and which can be separated by fractional distillation. These sterols are complex hydroaromatic secondary alcohols. Cholesterol contains an unsaturated carbon atom and its formula as slightly modified by Windaus and Heilbron, Simpson and Spring, from that suggested by Rosenheim and King, is shown in the following figure.



DISTRIBUTION OF CHOLESTEROL. Cholesterol is an essential constituent of all cells and fluids of the body. It exists in the free state and also combined with fatty acids as esters. These two forms are not equally distributed. In bile it occurs only in the free state and tends to vary with the amount in blood. In the corpuscles of human blood, cholesterol exists chiefly in the free state, while in the plasma more than half is present as the ester.

The free cholesterol content of tissue is characteristic and normally remains almost constant

TABLE 58
Distribution of cholesterol in blood
(After J. M. H. Campbell)

	WHOLE BLOOD	PLASMA	COR-PUSCLES
Total quantity, grams per 100 cc. of blood.....	0.18	0.09	0.09
Cholesterol as ester.....	0.06	0.05	0.01
Free cholesterol.....	0.12	0.04	0.08

TABLE 59
Average total cholesterol content of the normal tissues of the rabbit
(After E. Noble Chamberlain)

	GRAMS PER CENT
Suprarenals.....	7.3
Brain.....	1.8
Kidney.....	0.436
Spleen.....	0.38
Lung.....	0.376
Liver.....	0.285
Blood.....	0.078
Muscle.....	0.064

while the esters are subject to considerable variation in amount. The brain and suprarenals have the richest supply. In the former it is found mainly in the free form. (See table 58.)

In human liver the total cholesterol is about 0.24 per cent and in spleen 0.36 per cent (J. A. Gardner).

Table 59 shows the average total cholesterol content of the normal tissues of the rabbit.

ABSORPTION, TRANSPORT AND EXCRETION OF CHOLESTEROL. Cholesterol administered orally is absorbed in only small amounts unless some fatty material is also present in the intestine. Bile and pancreatic juice are said to aid in its absorption. Combination with the bile acids increases the solu-

bility of cholesterol in intestinal fluids. Cholesterol esters are hydrolyzed by pancreatic and intestinal enzymes. These esters are resynthesized reaching the lymph stream which is the main way by which cholesterol is absorbed. Some cholesterol is absorbed directly into the blood stream. It is very interesting that closely related sterols (ergosterol, coprosterol) are absorbed only in very small amounts (Schoenheimer and Sperry). The small intestine contains an enzyme which will split the ester, presumably, under other conditions, will synthesize (Shope; Sperry and Schoenheimer). Part of the absorbed free cholesterol but no cholesterol ester is excreted in the bile and part is changed to coprosterol by hydrogenation and eliminated in the feces. Some unchanged cholesterol is also excreted. The cholesterol plus coprosterol in the feces is usually greater than the cholesterol of the diet. Some of the biliary cholesterol is absorbed in the small intestine. Gardner and Gainsborough state that cholesterol can be found in normal urine and that the amount is increased by cholesterol feeding and in certain diseases. Under these circumstances cholesterol deposits may be found in the kidney tubules.

THE PHYSIOLOGICAL SIGNIFICANCE OF CHOLESTEROL. While there are numerous examples of the physico-chemical antagonism of cholesterol and lecithin very little can be said about the physiological importance of this relationship in the mammal. The interesting structure of the sterol molecule and the relationship to vitamins has been discussed elsewhere. The relationship of the sterols to the carcinogenic materials, hormones, the bile acids, the cardiac glucosides and possibly also to the so-called "organizer" in embryonic tissues provides fascinating material for speculation and stimulus for further work. Indeed, the probability that the bile acids, oestrogens, the corpus luteum hormone and the sex hormone may be prepared from cholesterol in the laboratory suggests that cholesterol may be the "mother substance" of these physiologically important compounds. If this is accomplished, cholesterol will be immediately invested with great physiological importance.

The increased cholesterol of the blood due to fat absorption is probably due in large part to the absorption of cholesterol contained in the pancreatic and intestinal juices and the bile. An increase in cholesterol ester has been taken to indicate that the sterol may play a part in the transport of fatty acids. The increase in cholesterol

ster in certain degenerative conditions of the has been referred to previously. The only by which atherosclerosis can be produced by dietary means is by feeding diets high cholesterol.² Feeding cholesterol is one of the certain means of producing excessive deposition of neutral fat in liver. Under these instances there is also a large accumulation of sterol esters. The increased amounts of sterol esters in liver when cholesterol is fed be a protective reaction and indicate that the is a less harmful form than the free cholesterol. The fatty liver produced by cholesterol is not so readily affected by lipotropic substances as deposition of fat produced by less measures.

The antilipotropic action of cholesterol, is in part at least, by a depression of the rate of phospholipid turnover in the liver. The effects of the various lipotropic factors on the rate of cholesterol esters in the liver is still studied, but choline and methionine appear to be more active than inositol.

It is thought that cholesterol is one of the constituents of bile which makes this substance so important in the emulsification of fats and therefore in their digestion and absorption. There is evidence that cholesterol can be synthesized in the liver since it may be excreted even when very little is obtained in the diet in mammals. Furthermore, it is present in the eggs of birds when the yolk contains little or none of the substance. There is an increase in blood cholesterol during pregnancy. It will be apparent from these remarks that there is a great deal to be learned concerning the physiological significance of the sterols.

THE ABSORPTION OF FAT

(See also p. 462)

The processes underlying the absorption of fat have long been a subject for debate and many aspects of the problem still remain obscure. It is now to be established that, except for small quantities which may be absorbed as a fine emulsion of unsplit fat, hydrolysis of the fat into constituent fatty acids and glycerine is a necessary preliminary to absorption. The possibility that small quantities of fat are transferred across the intestinal mucosa unchanged is suggested by the observation that paraffin oil (which of course is not digested) undergoes some slight absorption

in rabbits and guinea-pigs are the only animals in which atherosclerosis has been produced by this means.

(Channon and Collison). Lanolin, on the other hand, though it is well emulsified, is not absorbed. The view widely held some years ago, that fatty acids are absorbed in the form of soaps, is untenable, for any soaps which might be formed could not be held in solution in the acid fluids of the intestine. Verzár and his colleagues have been led to believe from their experiments that fatty acids form a complex with the bile salts (1 molecule of fatty acid to 3 of bile acid) which is water-soluble and readily diffusible. This power of bile salts to bring water-insoluble materials into solution in the intestinal juices is spoken of as their *hydrotropic action*. According to this conception the bile salt-fatty acid complex diffuses into the epithelial cells. After transference across the epithelial boundary it breaks down into its components, the fatty acid combines with glycerine which has diffused into the cell from the intestinal lumen while the bile salt is returned to the liver in the portal blood stream⁴ (p. 458). There is evidence that an intermediate stage in the resynthesis of the neutral fat is the formation of a "specific" phospholipid. Sinclair found that during fat absorption a change occurred in the composition (but not in the total quantity) of phospholipid in the intestinal mucosa. During fat absorption the fatty acids of this "specific" phospholipid are those of the food fat. After fat with a high iodine number (i.e., a highly unsaturated, e.g., cod-liver oil) has been fed, the phospholipid of the mucosa has a high iodine value also. The belief that phosphorylation of the fatty acid occurs as a step in the synthesis of neutral fat in the intestinal mucosa has been supported by Verzár, but serious doubt has now been cast on his evidence.

Pathway of absorption. Part of absorbed fat can be collected from the thoracic duct lymph. Several investigators have reported that some fat is absorbed directly into the portal system but this is still a very controversial point. Satisfactory data accounting for all the fat which disappears from the intestine have not yet been presented.

The mode of transfer of the neutral fat from the epithelial cells to the central lacteals also remains a matter for conjecture. The leucocytes have been credited with this function but most of the evidence is against their playing such a rôle (see Leach). During fat absorption the central lacteals show rhythmic contractions which evidently serve to

⁴There is recent evidence that some absorption of fatty acids may take place without the participation of the bile salts.

pump the chyle contained within them into the lymphatics tributary to the thoracic duct. Thus the absorbed fat is constantly propelled along the lymphatic channels of the mesentery. By dark ground illumination under the high power of the microscope, the absorbed fat can be observed in the blood as minute particles (less than 1μ in diameter) termed *chylomicrons* (fig. 236).

Fat is not only transported as chylomicrons but as phospholipids, cholesterol esters, and possibly as lipoproteins. The relative importance of these mechanisms is a subject for further research.

THE ELIMINATION OF FAT FROM THE BODY

There is no fat or phospholipid in the urine under normal conditions but the latter may appear in disease. There are only traces of fat in the secretion of the skin.

The fat content of the feces is normally between 6 and 12 per cent of the fat which is absorbed but as Sperry has pointed out this bears no relation to the foot fat. In dogs, even after five weeks or more on a fat-free diet, there are considerable amounts of fat in the feces. Some 60 per cent of this is neutral fat and 40 per cent fatty acids. A large part of this lipid excretion is composed of bacteria and cellular debris.

When the bile duct is ligated, large, light colored stools are usually observed as this procedure interferes greatly with fat absorption. Digestion is nearly complete, however, as is shown by the fact that the fat is excreted chiefly as fatty acids. Fatty stools are found also when the pancreatic ducts are tied although the absorption of fat is by no means completely prevented. When pancreatic lipase is excluded in this way the fat is excreted as glyceride rather than as fatty acids.

BLOOD FAT

An analysis of the fatty materials occurring in the plasma of human subjects has been made by Boyd. His results are given in table 60. The amount of these materials occurring in the plasma of animals in the post-absorptive state does not vary greatly under normal conditions. If, however, a sample of blood is withdrawn four to six hours after the ingestion of a large amount of fat such as olive oil or thick cream, a distinct milkiness of the plasma may be observed. This is due to the presence of the tiny microscopic fat particles—chylomicrons (fig. 236) which have been mentioned previously. The extent to which the amount of fat in the blood has increased may be determined

by counting these particles under a dark field microscope as well as by the chemical methods already described for other tissues. Such a alimentary lipemia, as it is called, has been observed both in man and in animals, although does not occur in all species. Great variations in the magnitude of the increase may be observed in a single individual under apparently identical experimental conditions. This is not surprising when we consider that the amount of fat present in the blood at any given instant will depend on the balance between the rate of absorption from the small intestine on one hand and the rate at which it is being utilized or laid down as adipose tissue on the other. The rate of absorption from the intestine will depend on such factors as the emptying time of the stomach and the degree of emulsification. The factors which determine whether

TABLE 60
Lipid constituents of plasma
(After Boyd)

	MILLIGRAMS PER 100 CC.
Total lipid.....	589
Total fatty acid.....	353
Neutral fat.....	154
Phospholipid.....	196
Free cholesterol.....	47
Cholesterol ester.....	192

fat is utilized or laid down as adipose tissue are as yet unknown. It is obvious, therefore, that the degree of alimentary lipemia cannot be used simply as an index of the rate at which fat is being absorbed. Although the increase in blood lipids which we have been discussing is due chiefly to neutral fat, changes in the other fractions have been observed also during fat absorption. The phospholipids as a rule show a small and somewhat irregular rise, the significance of which will become clearer when further work on labelled molecules has been completed.⁵ The changes in cholesterol are even more irregular, and may be due solely to cholesterol which is poured into the intestine when fat is being absorbed. It is possible that changes in cholesterol from the free to the esterified form may be of some significance, but at present there is no direct evidence for the participation of cholesterol in the early stages of fat metabolism.

⁵ The phospholipids of the plasma are, in large part, those which contain choline and their rate of turnover is increased by feeding choline (Chaikoff).

THE LIVER AND FAT METABOLISM

The main facts which indicate that liver plays a particularly important part in the metabolism of fat are the following: (1) the fatty acids combined as liver phospholipids and glycerides are more unsaturated than fatty acids found in other tissues. (2) Under a great variety of conditions neutral fat or cholesterol esters may accumulate in the liver to a very much greater extent than in any other tissue. (3) The liver is the principal if not the only site of formation of the ketone bodies. (4) The rate of phospholipid turnover in the liver is more rapid than in any other tissue, with the possible exception of the intestinal mucosa during fat absorption.

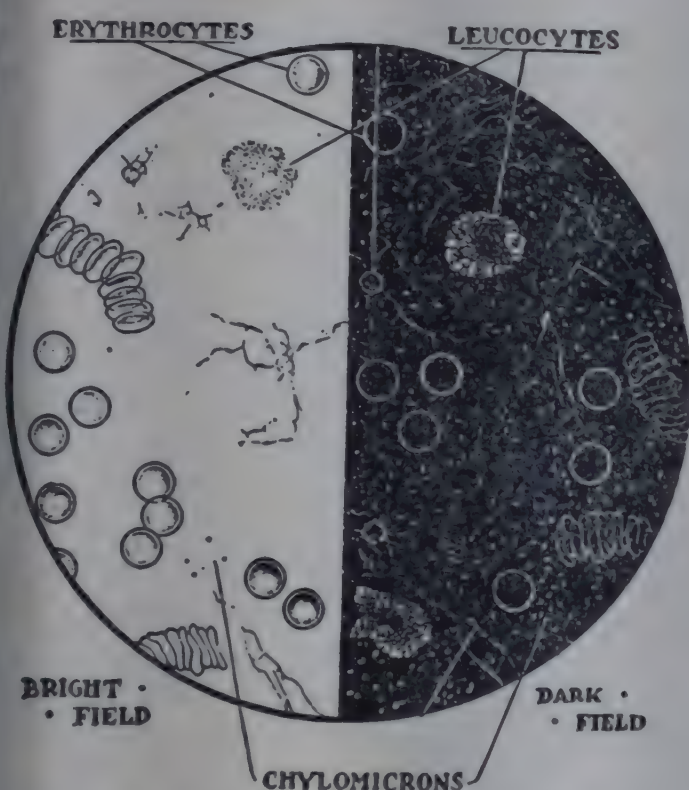


FIG. 236. Shows chylomicrons. (After Gage.)

(1) The fact that the phospholipid fatty acids of the liver are more unsaturated than those in other tissues suggests either that double bonds have been introduced into the fatty acid molecule in the liver (Leathes and Meyer-Wedell) or that the liver cells selectively retain the more unsaturated fatty acids (Raper). Using fatty acids "ear-marked" with deuterium, direct evidence of the desaturation of these acids in the body has recently been secured by Schoenheimer and Rittenberg, but further work is required to determine the rôle of the liver in this process.

(2) The various conditions which result in an excess of fat in the liver may be classified as follows:

1. Dietetic means—starvation, the feeding of diets rich in fat, or cholesterol, diets deficient

in choline, methionine, or other lipotropic factors.

2. Injection of substances obtained from the anterior pituitary gland.
3. Pregnancy, pernicious anemia, and diabetes.
4. Changes in atmospheric conditions—high and low temperature, low pressure.
5. Infectious processes.
6. Poisons—phosphorus, chloroform, benzol, phloridzin, etc.

The amount of fat which is present in the liver at any time depends on the following factors:

1. The rate at which fat is brought to the liver by the blood.
2. The rate at which the liver is able to take up fat from the blood.
3. The rate at which the liver can deal with fat, (a) by direct oxidation in the liver cells, (b) by passing it on in the same or in a slightly changed form to other parts of the body.
4. The possibility that fat may be synthesized in the liver from other materials.

There is an increase in the fat of the liver within a few hours after the ingestion of a meal containing large amounts of fat. Under these conditions the fatty acids of the liver glycerides and lipids are affected by those in the diet. Under other conditions when no fat is fed the liver may become intensely fatty, and here the fatty acids are derived from the depôt fat from ingested carbohydrate or protein. When "ear-marked" fats are deposited in the tissues and then some poison such as phosphorus or chloroform is administered the excess of liver fat contains the fatty acids which were present in the depôt fat. Cholesterol feeding causes a deposition of glyceride and cholesterol esters in the liver (Yuasa; Chanutin; Okey).

CHOLINE AND OTHER LIPOTROPIC⁶ FACTORS IN

FAT METABOLISM. Choline ($((\text{CH}_3)_3\text{N}-\text{CH}_2\text{CH}_2-\text{OH})$ which was first isolated from body fluid (bile) by Strecker in 1849 has long been known as a

⁶ The term lipotropic was originally used to describe the action of choline which prevented the deposition of, or accelerated the rate of removal of fat from the liver. It now has a somewhat broader meaning and is used to describe the action of other substances with a similar action on fat metabolism. Substances such as cholesterol which cause a deposition of liver fat are referred to as antilipotropic and diets free of lipotropic factors may be described as alipotropic. Cystine, under certain dietary conditions increases the deposition of liver fat and the incidence of hemorrhagic kidneys. This is apparently related to a stimulation of metabolism ather than to a direct antilipotropic effect.

component of lecithin and sphingomyelin. Its acetyl derivative, acetylcholine, has assumed a position of great physiological importance since the work of Lowei, Dale and others as discussed elsewhere. Choline, itself, has now been shown to be an important dietary factor, which exerts a profound effect on the storage and transport of fat in the animal body, on growth, and on various other physiological mechanisms.

In 1924 Allan, Bowie, Macleod and Robinson, and Fisher noted large fatty livers in insulin treated depancreatized dogs. This fatty change was prevented when raw beef pancreas was included in the diet. Hershey and Soskin noted a similar effect with crude egg lecithin and in studies on the fatty livers produced by dietary means in rats, Best, Hershey and Huntsman later identified the active component of lecithin as choline. This finding led to a long series of studies on the significance of choline as a dietary factor. Betaine and casein were found to exert effects similar to choline on the mobilization of fat (Best and Huntsman). Other proteins have since been found to be lipotropically active. The activity of casein is due in large part to its methionine content (Tucker and Eckstein). Methionine exerts its lipotropic action by transferring its methyl group to ethanolamine with the formation of choline (du Vigneaud; Stetten). Betaine also acts as a methyl donor (Stetten).

When these lipotropic factors are not available in the diet large amounts of fat accumulate in the liver. In young animals hemorrhagic lesions are seen in the kidneys and other tissues (Griffith and Wade), and these may produce death. The antilipotropic⁷ factor cholesterol aggravates the liver and kidney changes while choline, betaine and methionine prevent their development.

In depancreatized or normal dogs dietary conditions which permit fat to accumulate in the liver result eventually in cirrhosis of this organ (Chaikoff). In rats a hypolipotropic diet produces both necrosis and cirrhosis. These lesions which have been studied particularly by György and Goldblatt, Blumberg and McCollum, and Daft, Sebrell and Lillie, may be interrelated. Sebrell et al. have supplied evidence that choline prevents the cirrhosis; cystine, in small amounts, prevents the necrosis; and methionine which aids in the formation of choline in the body and also like cystine supplies sulphur, prevents both necrosis and cirrhosis. Furthermore, the acute effects of

chloroform poisoning on the liver in protein depleted dogs are diminished or prevented by the administration of methionine or choline plus cystine (Miller and Whipple).

The lipotropic action of choline has been studied by labelling the molecule with arsenic (Welch), radioactive phosphorus (in the lecithin) (Perlman and Chaikoff) and heavy nitrogen (Stetten). The results of all these studies indicate that choline accelerates the rate of phospholipid turnover in liver and kidney and to a lesser extent in other tissues.

In the depancreatized dog choline has been shown to be one of the active components of beef pancreas which as previously stated prevents the development of fatty livers. The protein of pancreas through its methionine content will presumably also exert a lipotropic effect. Furthermore, the pancreatic enzymes will help to liberate choline and methionine from the phospholipids and protein of the diet. Dragstedt and his colleagues have shown, however, that certain pancreatic extracts contain active materials other than choline and protein. It has been suggested by McHenry and Gavin that one of these may be inositol, which they have shown to be lipotropic in rats under certain conditions. Dragstedt and his colleagues find that inositol may exert a slight effect. They believe, however, that the pancreas contains another unidentified factor which affects the deposition of liver fat in depancreatized dogs. This view is also held by Montgomery, Entenman, Gibbs and Chaikoff, but they feel that the unidentified lipotropic factor is not the pancreatic hormone "lipocaic" postulated by Dragstedt.

FAT AND GLYCOGEN IN LIVER. While it is true that very small amounts of glycogen are present in very fatty livers and that the fat content is low when large amounts of glycogen are found, it can also be shown that moderate amounts of glycogen can accumulate in moderately fatty livers.

THE LIVER AND THE FORMATION OF KETONE BODIES. The main points of evidence that the ketone bodies are produced in the liver are as follows: (1) It was shown by Embden and Kalberlah that a liver perfused with long chain fatty acids with an even number of carbon atoms produced acetone. (2) Using the liver slice technique in the Warburg apparatus, Quastel and Wheatley showed that fatty acids with an even number of carbon atoms are broken down to the ketone bodies. (3) In a depancreatized dog showing a profound ketosis the ketone bodies in the blood

⁷ See footnote to page 601.

rapidly diminish after removal of the liver (Chaikoff and Soskin). (4) The rapid rise in the ketone body content of rabbit's blood produced when certain extracts of the anterior pituitary are injected is not observed after hepatectomy (Mirsky). (5) Substances which damage the liver frequently decrease ketosis.

OXIDATION OF FAT AND THE FORMATION OF KETONE BODIES. Although fatty acids are resistant to ordinary chemical oxidizing reagents, they are broken down completely to carbon dioxide and water in the body with the utmost facility.

acid molecules formed by this β -oxidation were rapidly broken down to carbon dioxide and water. Knoop's work was confirmed by Dakin who also studied the *in vitro* oxidation of the various fatty acids by H_2O_2 at body temperature. This data supported the theory of β -oxidation. Embden and his colleagues perfused various fatty acids through isolated livers and found that ketones were formed only from fatty acids with an even number of carbon atoms in the molecule. These findings taken together appeared to indicate that the last four carbon atoms in the fatty acid chain, under-

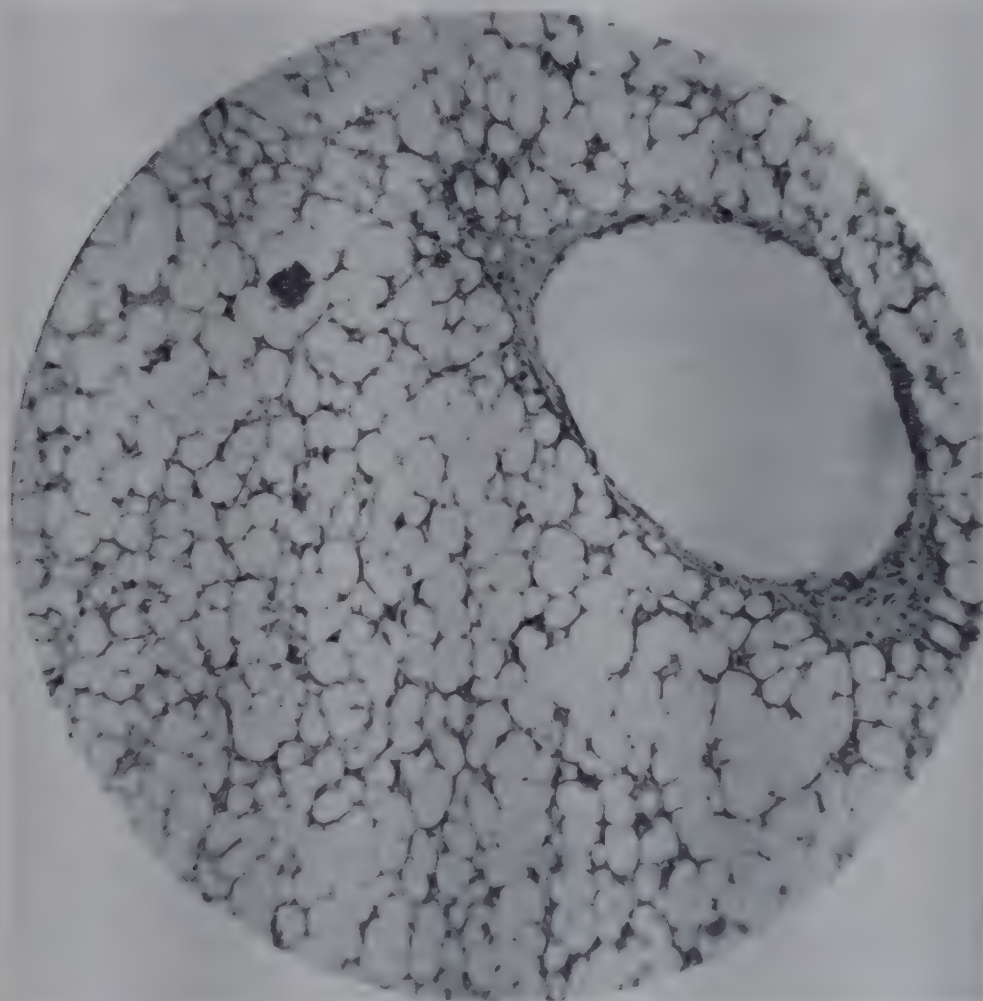


FIG. 237. Section from liver of depancreatized dog fed a diet low in choline. Ether-soluble material over 60 per cent of wet weight. $\times 200$. (From Best, Huntsman and Young.)

This made the detection of intermediate products extremely difficult and has been one reason for the slow progress of research in this field. The theory of successive β -oxidation which originated from the work of Knoop (1905) has occupied an extremely prominent position in the considerations of this subject. Knoop fed various phenyl substituted fatty acids to his test animals and identified the excretion products in the urine. The results were explained by assuming that the fatty acids were broken down by the splitting off of two carbon atoms at a time, i.e., by oxidation at the carbon atom which occupies the β -position to the carboxyl group. It was assumed that the acetic

went oxidation at the β -position but were not further degraded. Thus it was assumed that irrespective of the length of chain each even numbered fatty acid gave rise to one molecule of ketone.

In 1916 Hurtley tried to find the butyric and acetic acids which would be expected to be formed in the liver during active ketone formation. He was unable to find any trace of these acids. Several groups of workers who repeated the *in vitro* work of Dakin found that while β -oxidation did occur the oxygen could also become attached to the α and γ positions. In 1935 and 1936 Deuel and his collaborators found that more ketone bodies were formed in an animal fed octanoic acid than in one

given an equimolar amount of butyric acid. Jowett and Quastel, 1935, and Leloir and Muñoz, 1939, reported that the amount of ketone bodies formed by liver slices could not be accounted for on the assumption that only the last four carbon atoms of these fatty acids give rise to a ketone body as the theory of β -oxidation demanded. Blixenkrone-Møller, 1938, and Stadie, Zapp and Lukens, 1940 and 1941, studying perfused livers and liver slices *in vitro*, found that the oxygen consumption was far smaller than would be the case if all but the last four carbon atoms of each fatty acid were being broken down to acetic acid and this acid oxidized. The very important new fact had been established by the work of Jowett and Quastel, 1935; Edson, 1936; and Leloir and Muñoz, 1939, who worked on isolated tissues, and by MacKay, Wick and Barnum, 1940, who used intact animals. These investigators agree that the odd numbered fatty acids also give rise to smaller but significant amounts of the ketone bodies. Thus the theory of β -oxidation is not adequate to explain all the facts.

In 1916 Hurlley proposed the theory of multiple alternate oxidation to account for his failure to find butyric acids in livers where ketone formation was actively progressing. This theory required that the intact fatty acid chain be first oxidized at each alternate carbon atom and then split into blocks of four carbon atoms each. One molecule of palmitic acid $C_{16}H_{32}O_2$ would give rise to four molecules of aceto acetic acid.

Many workers, Jowett and Quastel, Brentano and Markees, Deuel and his collaborators, have found that fatty acids such as caprylic, capric or lauric acids would form more ketone bodies than either butyric or caproic acids in liver slices or in intact animals. The latter series possesses shorter carbon chains than the former. Blixenkrone-Møller, working with isolated liver of cats, reported that the fatty acids must be broken down to four carbon acids to explain the low oxygen to ketone body ratio which was observed. Stadie, Zapp and Lukens found that the mean value for the molecular ratio of oxygen uptake to the ketone body formation was very close to the value which could be expected if the average fatty acid $C_{16}H_{32}O_2$ was broken down to four molecules of aceto acetic acid. These authors also showed that the ratio of ketone body increase to that of fatty acid decrease, was very close to four.

The multiple alternate oxidation theory, however, implies a phenomenon which is rather

difficult to explain upon biochemical grounds. It is possible that the simultaneous oxidation of every alternate carbon atom in the fatty acid can take place but there is no reason why the molecule should be selectively split at every second keto group instead of at every one. Furthermore it was observed that odd-numbered fatty acids such as valeric acid $C_5H_{10}O_2$ could produce small amounts of ketone bodies when added to liver slices (Jowett and Quastel). It is known also that valeric acid can give rise to glucose through propionic acid and when this happens the two carbon atom fragment is left over. In order to explain why valeric acid can bring about the formation of ketone bodies it must be assumed that two of the acetic acid molecules condense to form acetoacetic acid. MacKay and his colleagues have conducted feeding experiments in intact animals which lend support to this interpretation. They have postulated a modification of the previously mentioned theories which they have named the " β -oxidation acetic acid condensation hypothesis". When propionic acid was fed to animals liver glycogen accumulated without the formation of ketone bodies. Valeric acid on the other hand led to both glycogen formation and the production of ketone bodies. According to MacKay's theory all fatty acids, whether they possess an odd or even number of carbon atoms, are oxidized at each alternate carbon atom. The molecule then splits at every keto group to form acetic acid molecules except where a three-carbon chain remains as propionic acid. This latter residue could be converted to carbohydrate via either lactic acid or succinic acid. It has been shown that acetic acid can condense to form ketone bodies, (Friedmann, 1913). The hypothesis of MacKay, Wick and Barnum, 1940 offers the most satisfactory explanation for the facts as we now know them.

INTERRELATIONSHIP OF THE KETONE BODIES
It is now believed that acetoacetic is the first of the ketone bodies to be formed. This acid may be reduced to β -hydroxybutyric in various mammalian tissues and the reverse process also takes place. Acetone is formed readily in biological fluids containing acetoacetic acid and this process presumably accounts for its presence.

SOURCE AND SITE OF FORMATION OF KETONE BODIES. Embden, Salomon and Schmidt (1906) found that the ketone bodies were formed in perfused livers when fatty acids, certain amino acids or pyruvic acid were added to the perfusate. This finding has been repeatedly confirmed. Fat, how

and the conditions in which there is an excessive deposition of fat in the liver (p. 601) are discussed elsewhere. A profound disturbance of phospholipid metabolism occurs in Niemann-Pick's disease, a condition which is seen in infancy and in early childhood and is invariably fatal. The spleen and liver are enormously enlarged and contain very large amounts of phospholipids. The cholesterol content of these tissues is also increased but not to nearly the same degree. The blood phospholipid is also definitely raised. Histologically there is a great hypertrophy of the reticulo-endothelial system. Very little is known about this disease but it has been suggested that there is some interference with the activity of the enzymes which are responsible for various stages of fat metabolism in the tissues.

In 1893 Hand described a condition in children which was characterized at autopsy by yellow nodules in the cranial bones and in other situations. Since it will become increasingly difficult to add more names when further cases are described it may be expedient to call the syndrome Hand's disease (Hand-Schuller-

Christian, etc.). While these nodules show a predilection for the tissues of the head, i.e., cranial bones, orbit, tuber cinereum, they have been noted in most portions of the skeleton (Chester and Kugel). The signs and symptoms depend on the areas affected. Diabetes insipidus and exophthalmos are common disturbances, i.e., due to lesions near the pituitary gland and in the orbit. Rowland believes that the condition is due to an osseous form of xanthomatosis. These xanthomatous nodules contain large amounts of cholesterol and cholesterol esters, which together may account for a large proportion of their total fat. There is no alteration in the fat content of the unaffected parts of the body. The etiology of the disease is unknown. The generalized xanthomatosis, which is sometimes seen in diabetes mellitus, may disappear when the blood fats are reduced to normal values by appropriate treatment of the diabetic condition.

There is an increased amount of kersin in the spleen in Gaucher's disease.

A great deal of attention is being paid at the present time to the metabolism of fat in tumor tissue but no review will be attempted here. The important part played by cholesterol in the formation of gall-stones has been dealt with (p. 467).

CHAPTER LII

THE METABOLISM IN STARVATION (FASTING), OBESITY AND UNDERNUTRITION

STARVATION

An animal deprived of food derives energy first from the combustion of its own carbohydrate stores (glycogen). Next, the fat reserves are drawn upon and finally, after these have been exhausted, tissue protein is broken down, the fatty acid part of the molecule is burned while the nitrogen is excreted in the urine as urea. The metabolism of several professional fasters has been investigated. Among the most famous of these are Succi, whose metabolism was studied by Luciani and others, Cette, investigated by Munk and Zuntz, Levanzin by Benedict and Beauté by Cathcart. One of the longest of such fasts upon record is that of Merlatte of Paris which lasted for 50 days. A dog has been starved for 117 days. By the end of this time it had lost 63 per cent of its weight, but was fairly active. Succi on the 40th day of his fast had lost about 25 per cent of his weight. The length of time a man could survive would depend largely upon his physical condition (fat stores, etc.) at the commencement of the fast, but it would probably not exceed 9 or 10 weeks in any event. Terence MacSwiney, Mayor of Cork, after his arrest during the Irish troubles in 1920, went upon a hunger strike which lasted 74 days; it was terminated by his death in coma.

During starvation the loss of weight is not distributed evenly throughout the body, some organs and tissues losing a much greater proportion of their weight than others (fig. 238). During the first few days the subcutaneous tissues and other fat depots bear the brunt of the effect of the fast. Large quantities of extracellular water are also lost at this time. Later, dissolution of muscular tissue occurs, as indicated by the N:S ratio of the urine (about 14:1). The water lost during this period is derived mainly from intracellular sources. Even in prolonged starvation the brain and heart lose a very small proportion (between 3 and 4 per cent) of their weight.

NITROGEN EXCRETION. *The total output of nitrogen* in the urine falls for the first day or two of the fast when the body is subsisting upon its carbohydrate supplies (p. 554). The length of this period varies, of course, with the size of the

carbohydrate stores at the commencement of the fast. A steady rise in nitrogen excretion follows, and usually reaches a maximum about the third or fourth day, but from then on it shows a progressive decline and may reach a value of less than 6 grams per day. The nitrogen excreted during the earlier part of the fast is apparently derived largely from the mobilization of "deposit protein" (p. 546). The *urea nitrogen* excretion at first rises, then falls; its percentage of the total nitrogen excretion also diminishes. The *ammonia* excretion rises. The *creatinine* output shows a steady decline but this is largely compensated for by the appearance of creatine (p. 550) so that the creatinine + creatine excretion remains fairly constant. The total output of nitrogen shows a pronounced rise shortly before death—the so-called *pre-mortal* rise. This probably indicates the exhaustion of the fat stores and the greater utilization of body protein for energy purposes. The total quantity of body protein catabolized may be determined by calculation from the total nitrogen excretion on the assumption that tissue protein contains 16 per cent of nitrogen and that practically all the nitrogen derived from the break-down of body protein appears in the urine. That is, each gram of urinary nitrogen represents the deamination of 6.25 grams of protein, so the quantity of protein broken down is calculated by multiplying the figure for the nitrogen excretion by 6.25. On this basis the average daily loss of body protein of an average sized man during starvation is about 50 grams or about 0.4 per cent of the total amount in his body. For a few days following the termination of a prolonged fast the nitrogen excretion shows a pronounced fall—nitrogen is retained for the reconstruction of tissue protein.¹

PHOSPHORUS AND SULPHUR. The urinary excretion of these elements shows an initial rise, and then a gradual decline, thus showing a curve

¹ The loss of protein varies widely among different organs and tissues. Addis and his colleagues found that in rats fasted for 7 days the several tissues contributed to the total protein loss in the following proportions, muscles and skin 62 per cent, liver 16 per cent, alimentary tract, spleen and pancreas 14 per cent, blood 6 per cent, kidneys 1 per cent, heart 0.5 per cent and the remaining organs 0.5 per cent.

which roughly parallels that of the total nitrogen excretion. Toward the latter part of the fast

the N:P and N:S ratios are around 5.3:1 and 14:1 respectively, i.e., approximately the ratio of these elements in muscular tissue.

The excretions of *chlorine, sodium, potassium* and *calcium* are reduced after the first few days of the fast but the normal levels of these minerals in the blood are maintained and their concentrations are much lower in the urine than in the body fluids and tissues, evidence that they are conserved. In the early days of the fasting period the sodium of the urine exceeds the potassium, indicating that extracellular water is being discharged (p. 18). Later the sodium, potassium and magnesium are in about the same relative concentrations in the urine as in the solid tissues; they are probably derived from the break-down of the latter. The calcium excretion is relatively large, indicating some dissolution of bony structures.

ACIDOSIS. The increase in urinary ammonium (p. 392) is a result of the production of excessive amounts of acid metabolites, especially β -hydroxy

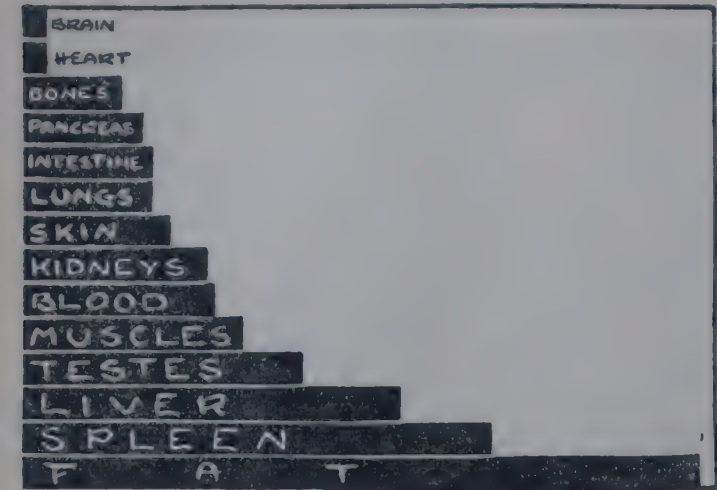


FIG. 238. Diagram showing the relative loss of weight of various organs during starvation as percentages of their initial weights. Contrast the loss of 97 per cent of the weight of body fat with the diminution of only 3 per cent in the weight of the brain; and the loss of 31 per cent of the weight of the skeletal muscles with a loss of only 3 per cent of the weight of the heart. (After Parsons, constructed from Voit's data.)

TABLE 62

Subject L. Height, 170.7 cm. Only distilled water was taken during this fast
(Abridged, after Benedict)

	DAY OF FASTING			
	1st	11th	21st	31st
Body weight, kg.....	59.60	53.88	50.49	47.39
Rectal temperature at 7 a.m.....		36.54	36.04	35.96
Pulse-rate, morning, awake.....	74	61	59	60
Urine:				
Total solids, grams.....	43.51	42.05	31.88	27.07
Total N.....	7.10	10.25	7.93	6.94
Urea N.....	5.68	7.66	5.54	4.84
Ammonia N.....	0.41	1.58	1.57	1.24
Uric acid N.....	0.112	0.116	0.112	0.122
Creatinine + Creatine N.....	0.48	0.49	0.38	0.32
Chlorine.....	3.77	0.36	0.18	0.13
P ₂ O ₅	1.66	1.95	1.60	1.32
N:P ₂ O ₅ ratio.....	4.28	5.26	4.96	5.26
S.....	0.46	0.62	0.51	0.49
N:S ratio.....	15.4	16.5	15.5	14.2
β -oxybutyric acid.....		1.4	5.0	4.5
Ca.....	0.217	0.220	0.237	0.138
Mg.....	0.046	0.072	0.053	0.052
K.....	1.630	1.006	0.644	0.606
Na.....	2.070	0.100	0.066	0.053
Loss of flesh calculated from N loss.....	213	308	238	208
R.Q., night.....	0.78	0.72	0.73	0.72
Calories, indirect, twenty-four hours' complete rest.....	1441	1193	1032	1072*
Calories per square meter (DuBois), twenty-four hours.....	843	732	653	701†

* Previous day = 1025.
† Previous day = 661.

butyric and acetoacetic acids. The latter are formed as a result of the carbohydrate deprivation, and the consequent incomplete combustion of fat. Succi toward the end of his fast excreted, daily, from 7 to 13 grams of acetone bodies. In a fasting, very obese, female subject (237 pounds, 4 feet 1 inch tall) reported by Folin and Denis the acidosis was extreme, some 18 grams of β -hydroxybutyric acid being excreted upon the fourth day of the fast.

CARBOHYDRATE METABOLISM. Even in the later stages of the fast glycogen is found in the liver, and the blood sugar is little depressed. Sugar is apparently synthesized from protein. In the earlier stages there may be a temporary hypoglycemia.

The *basal metabolic rate*, the *body temperature*, *pulse rate* and *blood pressure* all show a progressive fall throughout the fasting period. See table 62.

OBESITY

Some forms of obesity are due to a hypothalamic disorder (p. 884); to disease of the pituitary (p. 737, 740) or adrenal cortex (p. 698); or to hypofunction of the gonads. The increase in weight following the menopause, ovariectomy or castration is well known. In other instances obesity may be traced to subnormal thyroid function. These types of obesity are termed *endogenous*. The common type of obesity is usually the result simply of the consumption of a diet possessing a caloric value in excess of the energy requirements of the individual, a part of the excess energy of the food being stored as adipose tissue. The fundamental cause of this type is, therefore, overnutrition. Bluntly expressed, the subject eats too much for the exercise he takes. Obesity of such a type is, therefore, termed *simple*, *exogenous* or *alimentary*.

It must be remembered that the law of the conservation of energy holds for the animal body (p. 523). The energy taken in the food is either expended or stored within the body in the form of carbohydrate, protein or fat. So, whether the obesity is endogenous or exogenous it is due to an energy intake in excess of the expenditure, the balance being stored as fat. In most cases of the endogenous type the metabolism is low, i.e., energy expenditure is reduced, and this, no doubt, is the important factor in the production of the obesity.

SIMPLE OBESITY

In certain cases falling into the class of simple obesity there appears to be a constitutional element and a familial tendency. An inherent inclination to fatness seems to be illustrated by the common observation that of two persons who eat about the same amount of food, and exercise to the same extent, one may remain thin or of normal weight while the other grows fat. Furthermore, the "spare" person may have a large appetite and remain underweight while the obese may diet himself and still be fat. In order to explain such cases it has been suggested that they are due to an inherited endocrine characteristic, i.e., that they are in part at least endogenous in nature. Yet if this were so, some evidence of it should be forthcoming from metabolic studies. On the contrary, the basal metabolic rate per unit of body surface of the subject of the common or simple type of obesity is within normal limits—that is, his energy expenditure at rest is not less than the normal. Nor is work performed more economically than usual by the obese; the reverse is probably true on account of the greater amount of inert adipose tissue. His greater storage of energy cannot therefore be explained upon this basis. It has been claimed that the specific dynamic action of food (p. 554) is reduced in cases of simple obesity; and it has been suggested that such a reduction, by conserving energy, may play a causative rôle. The smaller specific dynamic action which has been observed could, however, account for no more than a 3 per cent reduction in the total daily metabolism, and is quite inadequate as an explanation. An almost inappreciable increase in the caloric intake or a slightly reduced bodily activity would produce a much greater effect upon the energy exchange. For example, 10 grams of extra fat daily in the diet (e.g., a teaspoonful of butter) yielding 90 Calories, or 23 grams of sugar (about 2 teaspoonsful) would increase the caloric intake of a person of ordinary activity by 3 per cent or so, while a slow walk of a mile would increase the metabolism to a corresponding extent.

It is probable that a hereditary or constitutional factor, in the great majority of instances of ordinary obesity, is more apparent than real, and that a careful investigation of these cases with respect to food intake and muscular activity would reveal a positive energy balance. It is therefore likely that, when obesity shows a familial tendency, the inclination of members of

the same family to follow similar habits with respect to diet and exercise, rather than some inherited endocrine peculiarity, is responsible. Or again, traits which lead to obesity—over-indulgence of the appetite, or a distaste for muscular exertion may be inherited. Also, the obese person often, though not a “big eater,” indulges in highly concentrated food. It may, therefore, be said that though endocrine factors cannot be absolutely excluded in all instances of so-called simple obesity no factors other than diet and exercise are definitely known to exert an important influence.

SUMMARY. The fundamental cause of obesity of whatever type is an imbalance between energy intake and energy output.

I. *Endogenous obesity* is due to the lowered metabolism resulting from a disturbance in hypothalamic or endocrine function, e.g., gonads, pituitary or thyroid.

II. *Exogenous or simple obesity* is the result of maladjustments between food and exercise. It has not been demonstrated that a low basal metabolic rate is a factor in reducing the energy expenditure. Work is not performed more economically, nor is the reduction in the specific dynamic action of food an important influence in the production of simple obesity.

THE “COST” OF OBESITY. (1) Owing to the increased weight, muscular exertion places a greater load upon the heart and circulatory system. The incidence of arterial hypertension is relatively high in persons who are overweight. (2) Dissipation of heat by conduction and radiation (p. 623) is reduced through the heat-insulating effect of the mantle of subcutaneous fat. Sweating is in consequence more profuse. (3) Diabetes is more common in the obese than in persons of normal weight. Joslin refers to diabetes as “the fatman’s folly,” and to obesity as “the open door to diabetes.” (4) Persons who are grossly obese are said to be less resistant to infections and poorer surgical risks than those of normal weight. (5) The incidence of gallstones is relatively high in the obese; according to Baumann, 88 per cent of persons with gallstones are overweight. (6) *Life expectancy.* Insurance statistics show that overweight after the age of 35 years is associated with a death rate much higher than that of lean persons or of those of normal weight, a fact which has been pithily expressed in the phrase, “the longer the belt the shorter the life.”

GENERAL PRINCIPLES IN THE TREATMENT OF OBESITY. The basis of treatment should be, as already indicated, (a) reduction in the caloric intake and (b) increase in the energy expenditure through exercise. The dietary restrictions should not be extreme and should be made gradually. The extent to which the caloric intake should be reduced will depend upon the degree of obesity and the amount of exercise prescribed but it should never be pushed to the point where the protein of the subject’s tissues is drawn upon for energy purposes; nitrogen equilibrium should be maintained. Above all things a properly balanced diet should be devised and an adequate supply of vitamins and minerals provided. When the obesity is pronounced (body weight 25 per cent or more above normal), weight reduction is brought about by placing the subject upon a diet possessing a caloric value 40 or even 60 per cent below his energy requirement; he is thus forced to consume his own fat. The caloric value of human adipose tissue is about 3500 Calories per pound.² The total requirement of the average obese subject is around 2500 Calories per day. A reduction in the energy intake by 40 per cent of the requirement, that is, 1500 Calories, will therefore entail a weight loss of nearly a third of a pound per day. The subject is kept upon the restricted diet until the desired weight has been reached; his caloric intake is then adjusted to his requirement (see p. 663).

It is toward the restriction of the more concentrated forms of food that attention is particularly directed. It will be recalled that the caloric value of fat is more than twice that of carbohydrate. Also fatty foods, since they contain little or no water, are more concentrated than starchy materials. Lard, dripping, olive oil, etc., are 100 per cent fat, whereas the protein and carbohydrate of white bread amount together to only about 60 per cent of its fresh weight. Ordinary fats and oils should therefore be restricted. Butter, though about 85 per cent fat, should not be disallowed owing to its value as a source of vitamin A. Sugar in the form of sweetening for beverages, in jams, honey and chocolates is a highly concentrated food. By curtailing its consumption a large reduction in the caloric value of the diet can be effected without the disadvantage attending the reduction of some of the other foods. Bulky foods, e.g., green vegetables and salads of low caloric value but satisfying to the appetite may be substituted. Undue restriction of the water intake is sometimes practised but this measure appears to be of no benefit and may be a detriment to health. Alcohol has a high caloric value and is therefore, except in minimal amounts, excluded from the diet. *Thyroid extract* is sometimes employed to raise the metabolic rate and so reduce the obesity. The hormone is clearly indicated as a means of raising a low metabolic rate to

² Pure human fat has a caloric value of approximately 9.5 Cal. per gram. 3500 Cal. per pound here given is the value after allowance has been made for connective tissue and water content.

normal, otherwise its use is not to be advocated except in exceptional cases and only when the subject's basal metabolic rate can be followed by frequent determinations. *Dinitrophenol* is another agent which raises the metabolic rate and has been employed with success in the treatment of obesity. It is a dangerous drug unless given under the strictest supervision. Cataract has been reported following its use; liver injury may also result.

UNDERNUTRITION (INANITION)

If a diet possessing a caloric value considerably below the energy requirements of the individual is persisted in, as during famine, war blockade, extreme poverty, disease (e.g., stricture of the esophagus or pylorus) or improper feeding of infants, serious nutritional effects result. It must also be remembered that just as an intake of calories over the output will cause obesity so an energy expenditure in excess of the caloric intake will result in a loss of weight. Consequently a man who performs heavy work upon a diet which is adequate only for a sedentary worker will suffer from undernutrition. The economic or other conditions which lead to extreme reductions in the total caloric value of the diet obviously must also cause, as a rule, a reduction in the intake of vitamins, essential minerals and first class proteins. As a consequence, the incidence of specific deficiency disorders, e.g., stunting, xerophthalmia, rickets, osteomalacia, scurvy, etc., is also high when the caloric value of the diet is markedly lowered. These special aspects of undernutrition are dealt with in other chapters. The general

effects of inanition are those of chronic partial starvation. Among the chief of these are,

(1) Reduction in body weight—emaciation. The body attempts to make up the caloric deficiency by burning its own tissues. The loss of weight is due chiefly to loss of fat, but also in severe instances to a loss of protein. The nitrogen balance is negative. In children growth is retarded. The positive nitrogen balance is smaller than normal, it may even be negative. In the less severe grades of undernutrition in children the growth impulse continues to cause an increase in height of the skeleton but the muscles and the breadth of the body are poorly developed.

(2) Reduced B.M.R. down to 70 per cent or less of the normal, subnormal body temperature and lowered blood pressure. The subject is abnormally sensitive to cold, due to the fact that the skin vessels are constricted in an attempt to reduce the dissipation of heat through radiation and convection (p. 624). The skin temperature upon which our thermal sensations depend is therefore lowered. The specific dynamic response to food is increased.

(3) The subject is readily fatigued, there are mental apathy and a lack of a zest for physical exertion. Work is performed with the same expenditure of energy as normally, so, though energy is economized in the carrying on of the vital processes as shown by the reduced B.M.R. and cold skin, no economy is effected in the execution of muscular work.

(4) The loss of internal fat which normally serves to support the organs—stomach, kidneys, uterus, etc.—against the effect of gravity, results in their displacement (visceroptosis). The lost body fat is partially replaced by water.

(5) Susceptibility to infections, "Fever and plague dog the footsteps of famine."

(6) Depletion of the plasma protein with resulting edema (war or hunger edema).

CHAPTER LIII

METABOLISM IN MUSCULAR ACTIVITY

THE CHEMICAL PHYSIOLOGY OF MUSCULAR CONTRACTION

The mechanical response of an isolated muscle to stimulation is not accompanied by an increased consumption of oxygen; extra oxygen is not consumed until after contraction and relaxation are over. So, there are two phases in the contraction cycle, an *anaerobic (anoxidative) phase* and an *aerobic (oxidative) or recovery phase*, during which the muscle is restored to its previous state. If the muscle be stimulated repeatedly in an atmosphere of nitrogen it contracts forcibly at first, but soon becomes fatigued, since it cannot obtain the oxygen necessary for its recuperation between the individual contractions. Lactic acid accumulates and the muscle enters into rigor. If at the onset of fatigue, oxygen is re-admitted the lactic acid disappears, and the muscle recovers its original power to contract. The lactic acid concentration at which complete fatigue of skeletal muscle ensues (lactic acid maximum) is from 0.3 to 0.6 per cent. The lactic acid is derived from the breakdown of glycogen (p. 614). As the lactic acid concentration rises the carbohydrate stores diminish. Yet, the onset of fatigue is not due to the exhaustion of the glycogen stores, for the muscle fails to contract before the latter have disappeared. It is more likely that the high acidity inhibits the enzymes through whose action glycogen breakdown is brought about. Phosphoric acid also accumulates in a muscle contracting in the absence of oxygen. The phosphoric acid production rises rapidly during the earlier contractions, soon reaches a maximum and then ceases.

That a muscle can contract anaerobically has been known for many years. It has also long been known that lactic acid and CO_2 are produced by a muscle contracting in nitrogen. Spallanzani 150 years ago observed that snails placed in nitrogen evolved CO_2 . In spite of these earlier observations it was thought, nevertheless, that a muscle derived its energy from oxidative processes—for how otherwise was the CO_2 produced? In order to explain the phenomenon it was supposed (Hermann, Pflüger) that an oxygen store was contained in some giant molecule (termed “inogen” by Hermann) within the muscle substance itself. So “intramolecular” oxygen was spoken of as the hidden

oxygen reserve from which the muscle drew for its anaerobic contraction. Lactic acid also, it was thought, was derived from the breakdown of this hypothetical molecule. This theory was disproved by the classic experiments of Fletcher and Hopkins in 1907. These observers showed that the CO_2 which appeared during the anaerobic contraction was not the result of oxidation but was *preëxisting* CO_2 —i.e., simply CO_2 which had been liberated by the action of lactic acid upon sodium bicarbonate in the muscle fluids. They showed that the oxidative processes occurred after the contraction was over, that lactic acid then disappeared and CO_2 was formed. It was erroneously supposed at this time that the lactic acid which disappeared had been *completely* oxidized to CO_2 and water. That glycogen was the lactic acid precursor was indicated by the fact that the appearance of lactic acid in muscle fatigued in nitrogen was proportional to the glycogen loss. Also an R.Q. of around unity, found later by Meyerhof for the recovery phase of isolated muscle, indicated that its fuel was carbohydrate.

Meyerhof also showed that when oxygen was admitted to a fatigued frog's muscle, the amount of gas consumed was only one-fifth of that expected if the disappearance of the lactic acid were due to its oxidation to CO_2 and water. The heat produced during the oxidative phase was also much less than it should be were all the lactic acid burned. It was found, further, that glycogen *increased* in the fatigued muscle recovering in oxygen.

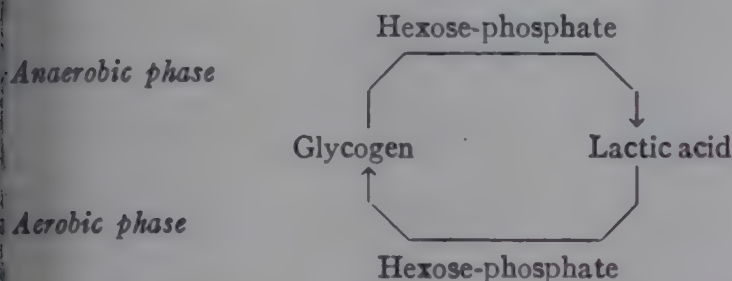
Embden had previously shown the importance of phosphate in the activity of muscle. Increased excretion of phosphate in the urine occurs as a result of muscular exercise, and Embden found that when muscle juice was incubated with a solution of bicarbonate lactic acid and free phosphoric acid appeared in nearly equimolecular amounts. He suggested that the *immediate* precursor of lactic acid was a hexose-phosphate. This he termed *lactacidogen*. A hexose-phosphate had been shown by Harden and Young to be formed as an intermediary in the fermentation of sugar by yeast. When Embden added this ester to muscle juice an increased formation of lactic and phosphoric acids occurred. He also claimed to have demonstrated an increased production of phosphoric acid in a muscle during its contraction. The phosphoric acid as well as the lactic acid was believed to be derived from the breakdown of *lactacidogen* (i.e., hexose-phosphate). It will presently be pointed out, however, that the phosphoric acid of muscle is derived mainly from phosphocreatine.

THE CARBOHYDRATE CYCLE

Before describing the other changes which occur during contraction a summary of what may be termed the carbohydrate cycle will be given.

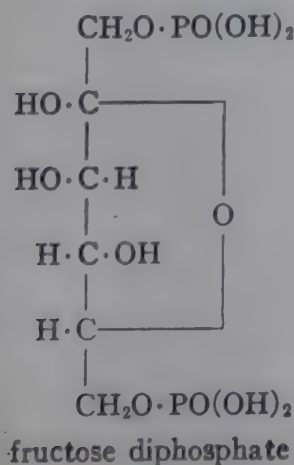
During the anaerobic phase of contraction, lactic acid is produced from glycogen through the intermediary of a phosphorus-sugar compound—hexose-phosphate.

In the recovery phase oxygen is consumed and about one-fifth of the lactic acid (or its equivalent) is oxidized, presumably to furnish energy for the resynthesis of the remaining four-fifths or so to glycogen.

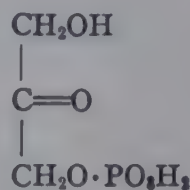


The intermediary reactions involved in the breakdown of glycogen to lactic acid are not shown in the foregoing scheme. Evidence for the anaerobic chemical changes about to be outlined has been obtained very largely from studies of the enzyme systems in aqueous extracts of muscle and in yeast juice during alcoholic fermentation.

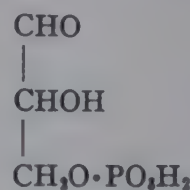
Through the action of the enzyme *phosphorylase* glycogen is broken down to glucose which undergoes esterification with inorganic phosphate to form glucose monophosphate—*glucose-1-phosphate*. *Adenosinetriphosphate* (ATP) acts as a co-enzyme (p. 615) in this reaction, giving up phosphate and being converted to *adenosinediphosphate* (ADP). Glucose-1-phosphate by intramolecular rearrangement is converted to *glucose-6-phosphate* through the action of *phosphoglucomutase*. Glucose-6-phosphate reacts with ADP, which gives up phosphate with the production of *adenylic acid* (adenosine monophosphate) and *fructose-1-6-diphosphate*.



Fructose diphosphate yields a molecule each of *dihydroxyacetone phosphate* and *3-phosphoglyceraldehyde*.

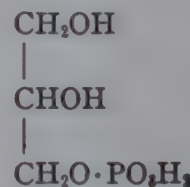


Dihydroxyacetone phosphoric acid

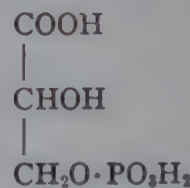


3-phosphoglyceraldehyde

Dihydroxyacetone phosphoric acid, through reduction, is converted to *glycerophosphate*; phosphoglyceraldehyde is oxidized to *phosphoglyceric acid*.

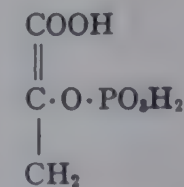


Glycerophosphoric acid



Phosphoglyceric acid

Phosphoglyceric acid is converted to *enol-phosphopyruvic acid*.

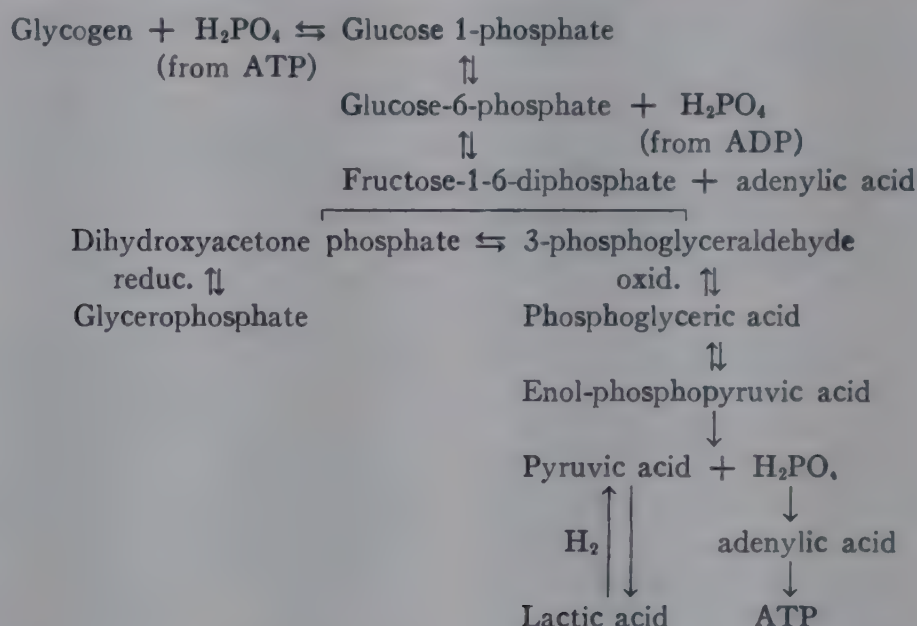


Enol-phosphopyruvic acid

Phosphopyruvic acid reacts with adenylic acid (formed, as mentioned above, in the phosphorylation of glycogen) with the production of pyruvic acid and ATP. The pyruvic acid reacts with phosphoglyceraldehyde through the action of *cozymase*, and is reduced to lactic acid; phosphoglyceraldehyde is oxidized to phosphoglyceric acid. As pyruvic acid is produced, it reacts with the phosphoglyceraldehyde which is furnished continuously during contraction by the breakdown of fructose diphosphate. The equilibrium dihydroxyacetone phosphate \rightleftharpoons phosphoglyceraldehyde,

shifts to the right when pyruvic acid first appears, there being little further production of dihydroxyacetone phosphoric acid.

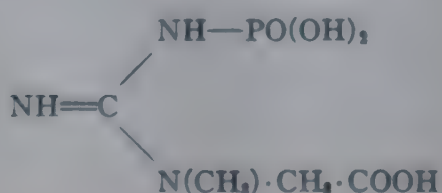
The reactions just described are summarized in the following scheme modified from Meyerhoff.



All these reactions are reversible, with the possible exception of that between enol-phosphopyruvic acid and adenylic acid and the formation of ATP. Evidence derived from the use of isotopic phosphorus is against this reaction being reversible.

THE RÔLE PLAYED BY PHOSPHOCREATINE (PHOSPHAGEN)

Until the last few years no reactions of importance other than those just given (the carbohydrate cycle) were believed to be associated with the contractile mechanism. The glycogen \rightarrow lactic acid conversion was considered to be the *immediate* source of muscular energy. This view has been revised as a result of the following observations. In 1927 Eggleton and Eggleton obtained from muscle an organic compound of phosphoric acid. During contraction this compound breaks down liberating phosphoric acid which in the absence of oxygen accumulates in the muscle. The Eggletons therefore called it *phosphagen*. Fiske and Subbarow about the same time isolated a compound of phosphoric acid which they called *phosphocreatine*. This is also known as creatine phosphoric acid and is identical with the phosphagen of the Eggletons. It has the following formula:



In the presence of oxygen the phosphoric acid and creatine are resynthesized to phosphagen. In the muscle deprived of oxygen the resynthesis is incomplete.

Phosphoarginine is the corresponding phosphagen in invertebrate muscle.

In the muscles of some species both compounds are present.

Contraction without lactic acid production

An experiment of Lundsgaard (1929) has revealed the essential importance of phosphocreatine in the contractile process. He found that after the injection of sodium iodoacetate into the dorsal lymph sac of a frog, violent contractions of the muscles occurred followed by rigor. When a muscle of the poisoned animal was isolated and stimulated electrically in nitrogen it responded, but *no lactic acid was produced*. After about 10 contractions, it became fatigued. This is much sooner than the onset of fatigue in normal muscle and, unlike the latter, the poisoned muscle became slightly *alkaline* in reaction. About 0.5 mg. of lactic acid per gram of tissue is formed in a normal muscle after a similar number of contractions.

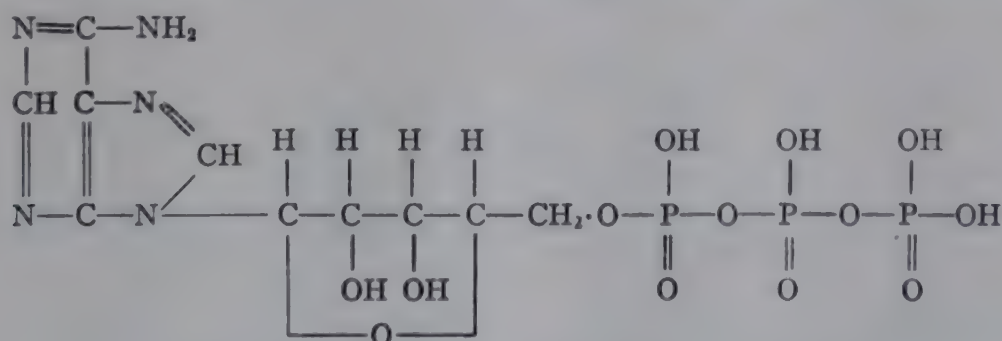
Upon analysis the poisoned muscle shows a loss of glycogen, and of phosphocreatine, and an increased content of hexose-phosphate. The lactic acid and phosphocreatine-phosphorus values of normal and poisoned muscles after 150 contractions each are shown in the following table (after Lundsgaard).

		Lactic acid mg. per cent	Phosphagen phosphorus mg. per cent
Normal	Resting.....	25	61
	Working.....	84	40
Poisoned	Resting.....	16	57
	Working.....	15	0

It was concluded that the greater quantity of phosphocreatine in the working normal as compared with the poisoned muscle was not the result of a reduced breakdown of this substance but rather of its resynthesis. The energy for resynthesis, it was suggested, was derived from the glycogen \rightarrow lactic breakdown. The energy which could be derived from the production of one gram of lactic acid, and its neutralization by the muscle proteins is 280 calories. In the foregoing experiment about 0.06 gram (61 mg.) of lactic acid was formed by the normal muscle. This exothermic reaction would therefore furnish $0.06 \times 280 = 16.8$ calories. In the resynthesis of phosphocreatine from phosphoric acid and creatine heat is absorbed (endothermic reaction). The resynthesis of 40 mg. as in the above experiment would require 16.5 calories, i.e., about the same quantity of heat as was given out in the production of 0.06 gram of lactic acid. Evidently, the reason for the complete disappearance of the phosphocreatine from the poisoned muscle is the failure of its resynthesis, and this in turn is due to the failure in lactic acid production. The breakdown of glycogen to hexosephosphate is not prevented by iodoacetic acid; the drug inhibits oxidation and reduction, hence dihydroxyacetone phosphoric acid breakdown is halted. Thus the poison destroys the carbohydrate mechanism which is essential for driving the phosphocreatine cycle. The poisoned muscle when stimulated in oxygen loses its phosphagen more slowly, and so fatigues less readily.

THE RÔLE PLAYED BY ADENOSINETRIPHOSPHATE ACID IN MUSCULAR CONTRACTION

Muscle contains the nucleotide (p. 565) adenosinetriphosphate (also called adenylyl pyrophosphate). This is a compound of adenine, d-ribose and three molecules of orthophosphoric acid. The following formula has been proposed for it by Lohmann.



Adenosinetriphosphate [Adenyl-pyrophosphoric acid]

It breaks down into one molecule of phosphoric acid and adenosinediphosphate. By the removal of a second molecule of phosphoric acid the latter is converted to adenylic acid (adenosinemonophosphate). A part of the latter undergoes deamination with the production of small amounts of ammonia and possibly of inosinic acid (hypoxanthine nucleotide). The decomposition of adenosinetriphosphate occurs at the very commencement of the contraction, i.e., preceding

the breakdown of glycogen. Though ammonia is liberated only in very small amounts, during moderate muscular activity, in fatigued or injured muscle as much as 3 mg. per gram of muscle may be produced.

The ammonia production and the breakdown of phosphocreatine into its components, which act as buffers (creatine and sodium phosphate being more alkaline than phosphocreatine) prevent the rise in acidity in the muscle fiber which otherwise might be expected to result during contraction. Actually, little change in reaction occurs. The slight but definite alkalinity noticeable in muscle poisoned with iodoacetate is due to the breakdown of phosphocreatine unaccompanied by lactic acid production.

Adenosinetriphosphate in the presence of Mg ions acts as a coenzyme serving as a donator and an acceptor of phosphate; in its absence phosphorylase is completely inactive. Adenosinetriphosphate when it breaks down yields adenosinediphosphate and phosphate for the esterification of glucose molecules derived from the breakdown of glycogen. Dephosphorylation of adenosinediphosphate, with the production of adenylic acid, is brought about by a separate reaction. Energy for the resynthesis of adenosinetriphosphate is derived from the breakdown of phosphocreatine which also furnishes the necessary phosphate. Energy and phosphate for the resynthesis of the latter are derived, it is believed, from the degradation of phosphopyruvate, ADP and ATP acting as intermediaries in the transference of phosphorus.

The muscle protein *myosin*, or some substance indistinguishable from it, was shown by Engelhardt and Ljubimowa in 1939 to act enzymatically, catalyzing the dephosphorylation of adenosinetriphosphate with the production of adenosinediphosphate. The degradation of the latter to adenylic acid and phosphate is caused by a different enzyme associated, apparently, with the soluble muscle proteins. Needham and his associates

have advanced a tentative theory based upon the surprising discovery that myosin, which it will be recalled composes the contractile fibrils of muscle, is an enzyme. They suggest that in the resting muscle adenosinediphosphate accepts phosphate from phosphocreatine to form adenosinetriphosphate; the latter then donates phosphate to myosin, the phosphorylated protein molecule then assuming the elongated or extended form. Upon excitation of the muscle myosin liberates

phosphate, the shortened or contracted form of the molecule then resulting. Myosin or *adenosinetriphosphatase*, as it may appropriately be called, is activated by Ca ions and to a less degree by manganese ions. Bailey suggests the possibility that the first effect of stimulation of muscle is to make activating Ca ions available for the myosin composing the contractile fibrils. This theory, though admittedly lacking in detail, arouses unusual interest since it attempts to link the chemical processes in muscle with the mechanical changes.

It is now widely believed that adenosinetriphosphate itself is the immediate source of the energy for contraction, and that it is resynthesized by the energy liberated in the subsequent breakdown of phosphocreatine.

SUMMARY OF THE CHEMICAL CHANGES ASSOCIATED WITH MUSCULAR CONTRACTION

The series of chemical changes which probably occurs may now be given in natural sequence. The first reactions are the breakdown of adenosinetriphosphate to *adenylic acid* and *phosphoric acid* which becomes engaged simultaneously in the phosphorylation of glycogen; fructose *diphosphate* is formed. *Phosphocreatine* next breaks down, yielding *creatine* and *phosphoric acid* which immediately joins with the adenylic acid formed in the previous reaction, adenosinetriphosphate being resynthesized. The fructose diphosphate gives rise to *dihydroxyacetone phosphoric acid* and phosphoglyceraldehyde, and the series of reactions of the carbohydrate cycle indicated on pp. 613 and 614 follows. The total energy derived from

oxidation of the remainder of the lactic acid. In fatigue, the accumulation of lactic acid slows and then arrests the glycogen \rightarrow lactic acid breakdown and, as a consequence, phosphocreatine resynthesis is prevented. Lactic acid production, therefore, though not directly furnishing the energy for contraction, serves to "wind up" the contractile mechanism or, if one may compare it to a storage battery, to recharge it. Adenosinetriphosphate is the immediate source of the energy for the contraction. The reversible reactions are dependent upon an enzyme system in the muscle; adenosinetriphosphate, in the presence of magnesium ions, acts as a co-enzyme serving as an intermediary in the transference of phosphate.

That the production of lactic acid is not the immediate source of the energy for contraction is proved by the following facts:

(a) Contraction of the muscle occurs before lactic acid is produced.

(b) A muscle, poisoned with iodoacetate, continues to contract for a time though no lactic acid is formed. Also, an unpoisoned muscle will contract after the glycogen stores have been exhausted.

(c) The greater part of the lactic acid is produced after the contraction is over, i.e., in the recovery phase, and it is probable that none is produced during the first one or two of a series of rapid twitches.

The energy exchanges are summarized in the following scheme:

(a) Adenosine triphosphate \rightarrow	phosphoric acid + adenylic acid	energy for contraction
(b) Phosphocreatine \rightarrow	creatine + phosphoric acid	energy for resynthesis of adenosine-triphosphate
(c) Glycogen to lactic acid		energy for resynthesis of phosphocreatine
(d) Oxidation of part of lactic acid (about $\frac{1}{2}$)		energy for resynthesis of the remainder of the lactic acid to glycogen

the conversion of glycogen to lactic acid is utilized for *phosphocreatine resynthesis* which takes place partly (about $\frac{1}{2}$) in the anaerobic phase and partly (about $\frac{1}{2}$) in the aerobic phase. The phosphoric acid for the resynthesized phosphocreatine is obtained from the breakdown of phosphopyruvic acid by way of adenosinetriphosphate. Thus phosphate borrowed from adenosinetriphosphate for the phosphorylation of glycogen is given up for the resynthesis of phosphocreatine. Of the lactic acid formed, a part is resynthesized to glycogen, the energy for the resynthesis being derived from the

Before concluding this account of the chemical changes underlying muscular contraction, the views of Sacks and his associates which are opposed to those of the Embden-Meyerhof-Lundsgaard school should be briefly mentioned.

Sacks denies that the anaerobic processes as revealed by analyses of cell-free extracts of isolated muscle, and upon which the Embden-Meyerhof-Lundsgaard scheme is largely based, give a true picture of what occurs in muscle with its circulation intact. He contends that the primary source of the energy for contraction is the oxidation of glycogen to lactic acid

without phosphorylation. That is to say, hexose-phosphate is not an intermediary in the formation of lactic acid except when the oxygen supply is inadequate. In the intact muscle the anaerobic mechanism is resorted to at the commencement of the contraction or at any other time that the circulation fails to supply the required amount of oxygen. During the steady state (p. 619) energy is furnished by direct oxidative reactions; anaerobic processes are then dispensed with. Sacks found that adenosinetriphosphate and phosphocreatine are resynthesised slowly, too slowly he believes to furnish energy for continued muscular activity. It is also claimed that the chief role of phosphocreatine is the neutralization of lactic acid. Furthermore, Sacks, using the radioactive isotope of phosphorus as a "label", could obtain no evidence of exchanges of phosphate between adenosinetriphosphate and phosphocreatine during the contraction of the cat's gastrocnemius under anaerobic conditions. He concludes that these substances do not act as intermediaries in the production of lactic acid within the muscle cell.

Some support for these views has been furnished by the experiments of Flock, Ingle and Bollman. They stimulated the weighted gastrocnemii of rats, circulation to the muscles remaining intact. The rate of stimulation was 3 per second. At the end of periods of stimulation, varying progressively in length, the muscles were rapidly frozen with carbon dioxide ice, fragmented and analyzed. During the first minute of work compounds associated with anaerobic activity, such as lactic acid, inorganic phosphate and hexose monophosphate accumulated rapidly; glycogen, phosphocreatine and adenosinetriphosphate decreased. The concentration of the last mentioned declined more slowly than the concentrations of the other two, a fact which the authors take as an indication that, contrary to the general belief, the hydrolysis of adenosinetriphosphate does not precede the breakdown of glycogen. As the work continued and a steady state was reached, the concentrations of adenosinetriphosphate and phosphocreatine remained unchanged; the concentrations of hexosemonophosphate and lactic acid returned to their resting levels. Flock and his associates conclude that the absence of any significant change in concentrations of the labile substances, once a steady state has been reached, gives evidence against their serving as a source of energy in continued muscular work. The removal of lactic acid they attribute to diffusion into the blood stream rather than to oxidation or resynthesis locally.

HEAT PRODUCTION IN MUSCLE

In the case of a muscle contracting isometrically, i.e., without shortening, all the energy which it expends appears as heat. If, on the other hand, the muscle is allowed to shorten and lift a weight, from 20 to 25 per cent of the total energy expenditure on the average, and under optimal conditions

30 per cent, appears as mechanical work. The efficiency of the muscular machine,

$$\frac{\text{mechanical work performed}}{\text{energy expenditure over the basal level (resting state)}}$$

is therefore much higher than that of the steam engine (7 to 20 per cent) and is comparable to that of the best types of gas engine (25 to 30 per cent).

The heat production of a muscle contracting isometrically in *nitrogen* shows four phases.

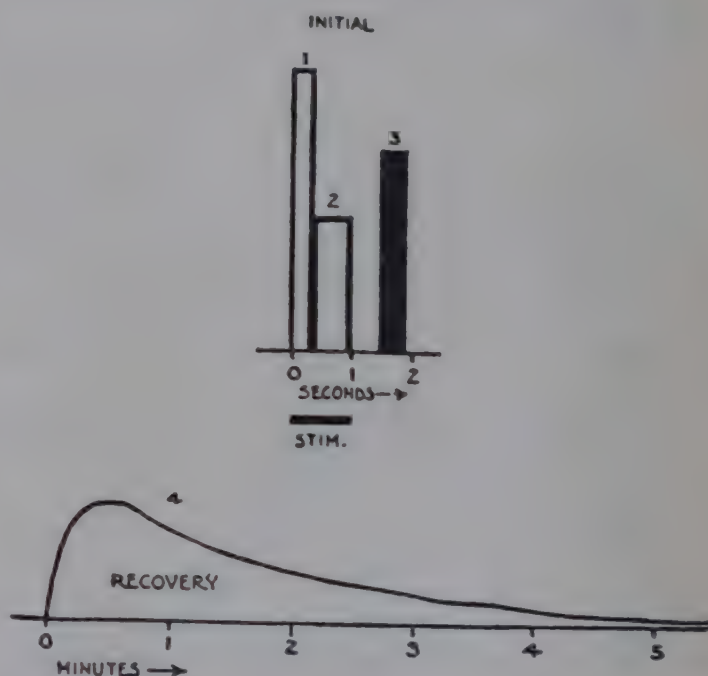


FIG. 239. Showing the stage of heat production of muscle during and following a short tetanic contraction. The first three stages represent the initial heat. 1, the contraction heat; 2, the heat produced during the maintenance of contraction; 3, the relaxation heat. The fourth stage (4) is the recovery heat. (From Evans, *Recent Advances in Physiology*.)

- (1) A large outburst of heat at the commencement of the contraction
- (2) A *sustained* heat production during contraction (tetanus)
- (3) A small outburst during relaxation—*relaxation heat*
- (4) A small amount of heat produced after contraction and relaxation are over. This so-called *delayed anaerobic* heat may continue to be produced for some considerable time.

The first three of these together are called the *initial heat* (figs. 239 and 240). In a single twitch (2) is not evident. The first outburst of heat and, in the case of a tetanus, the intermediary or sustained heat constitute the waste heat of chemical

reactions. The outburst during the relaxation or third phase is caused by the degradation to heat of the energy exhibited as tension during contraction; it amounts to about 35 per cent of the entire initial heat. This initial heat is also produced when a muscle contracts in oxygen but it is evolved in the anaerobic phase, i.e., it is independent of oxidative processes.

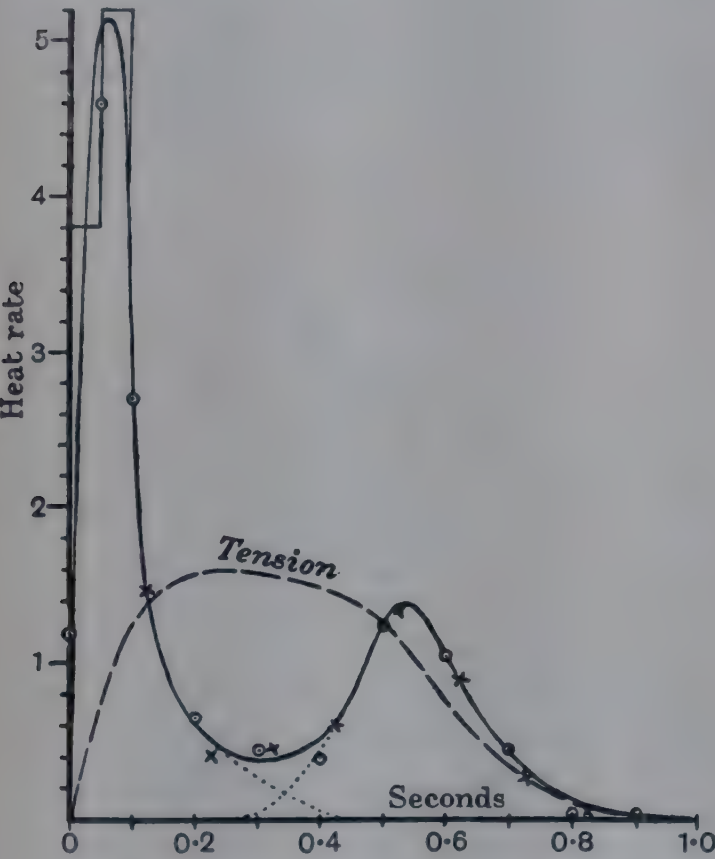


FIG. 240. Curve of initial heat developed in a single twitch at 0°C. The dotted line starting at 0.25 second, when the tension begins to fall, suggests the correct start for the heat due to mechanical relaxation.) After Hartree.)

The total heat production of a muscle contracting in oxygen is over 2.2 times greater than that of one contracting in nitrogen, for there is the added heat of oxidative processes—the *oxidative heat*. The delayed anaerobic heat plus the oxidative heat is referred to as the *recovery heat*. Thus the total heat evolved during normal contraction is made up as follows:

Initial heat:

- (1) Contraction heat
- (2) Relaxation heat

Recovery heat:

- (1) Delayed anaerobic heat i.e., heat of lactic acid production over that of phosphagen synthesis
- (2) Oxidative heat, i.e., heat of oxidative processes over that absorbed in resynthesis of glycogen

In a muscle poisoned with iodoacetic acid and contracting in nitrogen, the different phases of the initial heat and its total amount do not differ from those occurring in a normal muscle. Yet lactic acid production has been abolished. In such a case the initial heat production is apparently due mainly to the breakdown of phosphocreatine and adenylypyrophosphate—an explosive liberation of heat. In the normal muscle, on the other hand, lactic acid production and its neutralization by the muscle proteins causes a pronounced evolution of heat (exothermic reaction). Why then are the initial heats the same in both instances? Presumably, in the case of the normal muscle, the heat of lactic acid production and neutralization are masked being absorbed in the synthesis of phosphocreatine and adenylypyrophosphate (endothermic reaction). In either case it is believed that the initial heat represents the balance of heat production over heat absorption.

The recovery heat is also the resultant of exothermic and endothermic reactions—lactic acid oxidation and glycogen resynthesis. There is also the delayed anaerobic heat. It has been mentioned that a proportion of the lactic acid production occurs after the contraction is over, and that a proportion of the phosphocreatine resynthesis also occurs at this time. For a long time no explanation for the anaerobic delayed heat was forthcoming. It now appears that it, like the initial heat, represents a balance between the heat evolved during delayed lactic acid production and that absorbed by phosphagen resynthesis. The heat of recovery therefore is made up of this delayed anaerobic heat plus the balance between lactic acid oxidation and glycogen resynthesis.

MUSCULAR CONTRACTION IN THE INTACT ANIMAL

Oxygen debt

We have seen that an isolated muscle is able to contract when stimulated in an atmosphere of nitrogen but its recovery phase is postponed until oxygen is re-admitted. During strenuous exercise the muscles of the intact animal behave similarly. While contracting actively they are unable to obtain sufficient oxygen for the removal (by oxidation and resynthesis to glycogen,

arbitrary units	
(1) Contraction heat	0.65
(2) Relaxation heat	0.35
Total initial heat	1.0
(1) Delayed anaerobic heat i.e., heat of lactic acid production over that of phosphagen synthesis	0.08
(2) Oxidative heat, i.e., heat of oxidative processes over that absorbed in resynthesis of glycogen	1.16
Total recovery heat	1.24
Total heat	2.24

of the large quantities of lactic acid produced. Complete recovery must be postponed until the exercise is over, when the accumulated lactic acid is gradually removed. The muscles of the intact animal during strenuous exertion are therefore comparable to the isolated muscle contracting anaerobically. It was shown by A. V. Hill and his associates that an athlete during great muscular effort such as sprinting cannot possibly inhale more than a fraction of the oxygen required. That is, the body works its muscles but does not furnish them with the total oxygen required for the work until some time after this has been completed—it “goes into debt for oxygen” paying up during the recovery period (see fig. 241). In a hundred yard sprint, for example, the oxygen requirement may be over 6 liters. It is obviously impossible to deliver this amount to the muscle

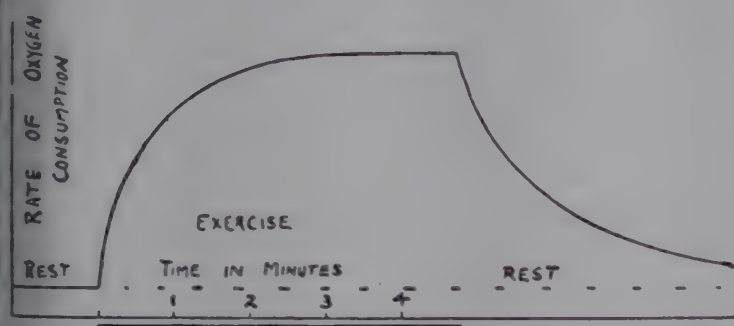


FIG. 241. Illustrating the increase in O_2 consumption above the resting level following exercise—“oxygen debt.” (From Hill, *Muscular Movement in Man*.)

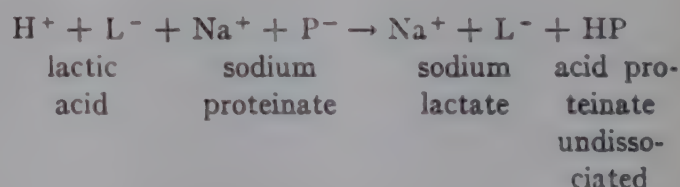
in the few seconds in which the race is run. The maximum consumption possible is not more than 4 liters of oxygen per minute. Furthermore, a sprinter can dash 100 yards with the breath held. The great value of the anaerobic phase of muscular contraction is thus revealed. Through the ability of the muscles to contract when deprived of oxygen and to replenish their stores of energy during the phase of oxidative recovery, they are enabled to perform for short periods an amount of work which otherwise would be impossible, that is, were they as in the case of a motor engine dependent entirely upon a contemporaneous oxygen supply.

The oxygen debt is determined by measuring the oxygen used during the period of recovery, i.e., from the termination of the exercise to the time when the oxygen consumption has returned to normal, and subtracting from it the quantity of oxygen used during a corresponding resting period. The length of the recovery period may be 80 minutes or more. In very severe exertion the oxygen debt amounts to over 10 liters (or about 0.3 cc. per gram of muscle tissue). The maximum

recorded in man is over 18 liters. During less strenuous exercise the discrepancy between lactic acid production and lactic acid removal is less pronounced, and the oxygen debt is correspondingly smaller. In light exercise the lactic acid is removed during the work—the body “pays as it goes,” and no oxygen debt is incurred. This is called the *steady state*. In other words, anaerobic and aerobic processes are balanced. The average man cannot maintain the steady state unless the oxygen requirement of the work does not exceed about 2 liters per minute. After severe exercise the normal level of lactic acid in the blood may not be reached until an hour or more after the exercise has ceased.

Lactic acid production during exercise

The lactic acid produced in a short bout of strenuous exercise may amount to as much as 3 grams per second, and its concentration in the blood rise as high as 0.2 per cent. The lactic acid, though buffered by the muscle protein thus



and to a less extent by phosphates and bicarbonates, causes a sufficient change in blood reaction to stimulate powerfully the respiratory center. Large amounts of carbon dioxide are “blown off” from the lungs.

Hill and Lupton have taken the excess oxygen consumed during recovery as a basis for calculating the quantity of lactic acid present in the body at the end of exercise. They assumed that the recovery oxygen was used entirely in the oxidative removal of lactic acid, and that the quantity of lactic acid removed by oxidation was, as in the case of isolated muscle, only about one-fifth of the total quantity which disappeared. Thus;



That is, for every 3 molecules of oxygen consumed during recovery 1 molecule of lactic acid has been oxidized, and for every molecule of lactic acid oxidized 4 have disappeared through synthesis to glycogen. Three gram molecules of oxygen consumed therefore represent the disappearance of 5 gram molecules ($90 \times 5 =$) 450 grams of lactic acid. Or, 1 gram molecule (22.4 liters) of oxygen represents the disappearance of $\frac{5}{3}$ gram molecules (150 grams) of lactic acid. Each liter of oxygen consumed during recovery would therefore indicate the disappearance of $\left(\frac{150}{22.4} = \right)$ 7 grams, approximately, of lactic acid.

The process of removal of the lactic acid is not confined to the muscles in which it arises. The liver, heart, brain and muscles not actually engaged in the exercise, share in the process the lactic acid being carried to them in the blood. Barr and Himwich showed this in animal experiments. From the results of their experiments upon rabbit muscle with intact nerve and blood supply, Sacks and Sacks conclude that, contrary to what is believed to occur in isolated frog muscle, lactic acid is not resynthesized to glycogen in the mammalian muscle during recovery, but diffuses into the circulation to be mainly converted in the liver to glycogen. A smaller part is oxidized by brain,

to the Ringer's something like 10,000 twitches can be evoked and a total tension of 6 tons per square centimeter of cross section of the muscle developed. It cannot, however, be concluded from experiments upon the isolated frog muscle, which for one thing is poorly supplied with oxygen, that the muscle of the intact mammal can use only carbohydrate fuel. Himwich and Rose, for example, by determinations of CO_2 and of O_2 of venous and arterial bloods of intact muscles obtained an average R.Q. of only 0.80. Attempts to decide the question for the intact body have been made by determinations of the respiratory quotient of the *excess metabolism of exercise* in man. The results are

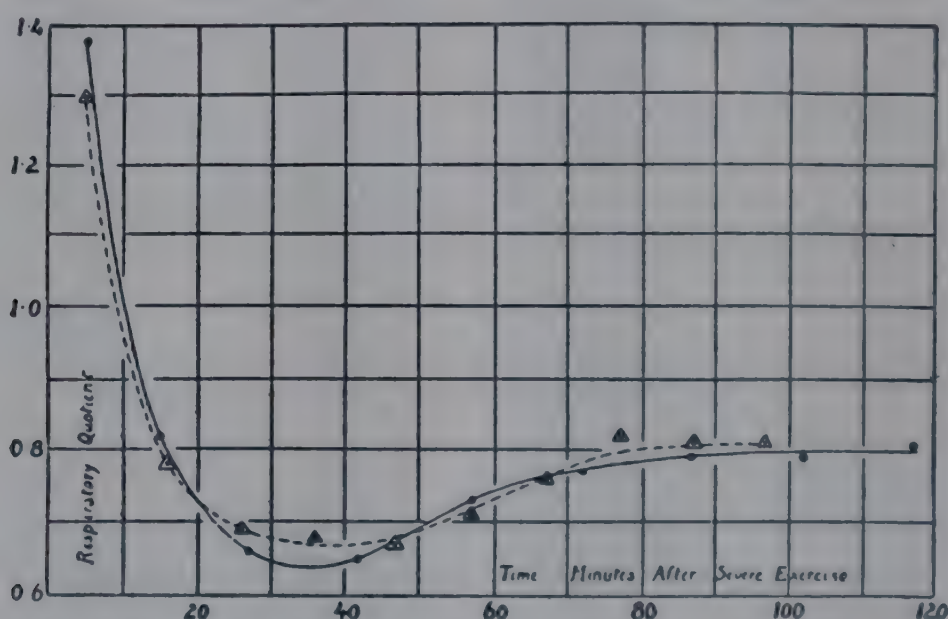


FIG. 242. Curve of the R.Q. of the excess metabolism caused by muscular exercise. (From Hill, *Muscular Movement in Man*.)

heart and probably by other tissues as well. If produced in large amounts, as in strenuous exercise, an appreciable amount finds its way into the urine.

The fuel of exercise

We have seen that in the case of isolated frog muscle the respiratory quotient is around unity, which indicates that the ultimate source of the energy for the contractile process is mainly if not entirely carbohydrate. That is, the energy required to restore the muscle to its pre-contraction state is derived from the oxidation of this food material. Though the glycogen of the isolated muscle is reduced by activity no diminution of its fat content has been demonstrated. It has also been shown that if an isolated muscle be stimulated while suspended in Ringer's solution so that the lactic acid as it forms may diffuse away, fatigue sets in only when the glycogen stores have been exhausted (see p. 612). If glucose be added

however, difficult to interpret and no definite conclusion can be drawn from them.

The excess metabolism of exercise is determined from the oxygen consumed (or of the CO_2 eliminated) during the work and recovery periods less the amount of oxygen used (or CO_2 eliminated) during a corresponding period preceding the exercise. The ratio between the excess quantities of the two respiratory gases will, of course, be the respiratory quotient of the excess gaseous exchange. But certain precautions must be taken in order to obtain the true respiratory quotient, i.e., the respiratory quotient of the oxidative processes, for as already mentioned a large proportion of the CO_2 which is eliminated following exercise is not oxidative in origin but is simply gas which has been liberated from chemical combination (p. 612). The period of increased CO_2 elimination and high R.Q. immediately following the exercise is followed by one in which the output of the gas is reduced and the R.Q. is well below the normal level of 0.85— CO_2 is being retained to replenish the bicarbonate stores (fig. 242). During a period of sufficient length, therefore, one effect (retention) will

st balance the other (blowing off) and the quantity of O_2 eliminated during this time in excess of the output during a pre-exercise period will be the extra quantity actually produced by oxidative processes. This value is used in calculating the R.Q. of the excess metabolism resulting from the exercise.

In experiments on man involving short periods of strenuous exercise, the R.Q. of the excess metabolism has been found by several observers to rise above that of the resting period and to reach or exceed unity. For example, Rest, Furusawa and Ridout obtained a respiratory quotient of between 1.18 and 1.68 for very arduous exercise. For less strenuous work the R.Q. was around unity and for mild exercise it was considerably lower—little above that for the rest period. The degree of exercise required to raise the quotient to unity varied in different subjects. The very high quotients (above unity) which these observers obtained have since been observed by others, but Gemmill in more rigidly controlled experiments in which the subject was kept under basal conditions for a period of several hours preceding the exercise, obtained an average respiratory quotient for the excess metabolism of a little less than unity. Determinations of the oxygen consumption and carbon dioxide elimination were made over a recovery (post-exercise) period of 3 hours.

The R.Q. of the excess metabolism has also been determined by several workers upon diets high, respectively, in fat or carbohydrate. Benedict and Cathcart, for example, found an R.Q. of 0.90 on a carbohydrate-rich diet and one of 0.82 (indicating the utilization of fat) on the fat-rich diet. They concluded that the fuel of exercise was not exclusively carbohydrate but depended largely upon the previous diet. Krogh and Lindhard decided that the food material oxidized during work was the same as that during rest and that in either case the relative quantities of fat and carbohydrate oxidized varied with their proportions in the diet. Work, however, was performed less economically (by 10 per cent) upon fat than upon carbohydrate.

Carpenter and Fox carried out two comparable groups of experiments. In one group 50 grams of glucose were given just prior to the commencement of the exercise. In the other group the subjects were fasting. The R.Q. of the excess metabolism of those which had received the glucose was considerably higher than those of the other group.

Anderson and Lusk obtained in a starving dog working a treadmill respiratory quotients suggestive of the combustion of fat, namely, from 0.71 to 0.73. Also in prolonged severe exercise in man Talbot and associates observed a fall in the R.Q. following an earlier rise.

Other lines of approach have yielded more important evidence for carbohydrate being the main fuel, though not necessarily the only one, used in muscular work. Other food-stuffs, especially fat can serve under certain circumstances, the propor-

tion of each which undergoes oxidation varying with the amount available and the severity of the exercise. In *short periods of light exercise* it is probable that the energy is derived from the oxidation of materials of the same nature as those which furnish energy during rest. These are small molecules of carbohydrate, fat and protein material already present in the circulation (Carpenter). Such materials are soon exhausted, however, by heavier work when the glycogen reserves are drawn upon. In *short and strenuous* bouts of exercise there is general agreement that the main fuel burned is carbohydrate. In a marathon race, for example, the call made upon the available sugar may result in hypoglycemia, and in endurance tests with animals it has been found that those given sugar can perform about three times as much work as they are capable of when on an ordinary diet. The administration of glucose at the commencement of the race prevents the fall in blood sugar and exerts a definitely beneficial effect upon the athlete's performance. The production of large quantities of lactic acid in strenuous muscular exercise also points to carbohydrate material as the source of energy. In *prolonged exhausting exercise* the carbohydrate stores become depleted; fat is then used largely to drive the muscular machine; the R.Q. falls. It is likely that the fat is oxidized directly and need not be converted first to carbohydrate. It is still uncertain whether such a conversion occurs.

The use of protein as fuel has been a subject of controversy for a number of years. It has been common teaching that this food material, except in minimal quantities when fat and carbohydrate are unavailable is not a source of energy for muscular work, but served merely to repair tissue "wear and tear." This conclusion was arrived at chiefly from studies of the nitrogen excretion. Ordinary exercise, for example, does not increase appreciably the output of nitrogen in the urine nor does it increase the non-protein nitrogen of the blood. More strenuous work causes a slight rise in the blood non-protein nitrogen and a moderate increase in the urinary nitrogen in man and in animals. In work experiments upon fasting dogs it has been calculated that at the most not more than 7 per cent of the energy required for the exercise could have been derived from protein; the great part of the energy had apparently been obtained from the combustion of fat. In prolonged starvation after exhaustion of the stores of carbohydrate and fat, protein (carbon part of the amino acids) must then, of course, serve as the sole source of energy.

It has been pointed out by Cathcart, however, that the nitrogen excretion during short periods of exercise

may not be a true criterion of protein metabolism since the nitrogen released in the breakdown of protein may be utilized in synthetic processes and consequently not appear in the urine. Or, muscle protein may be catabolized and its nitrogen excreted, yet if, as is quite possible, an equivalent amount of nitrogen derived from the food were diverted to the muscles to replace that which had been lost, the total nitrogen excretion would remain unchanged. This observer also considers that, in the long run, muscular work exerts a very definite influence upon protein metabolism and cites the familiar observation that persons engaged in heavy muscular work demand a diet rich in protein, particularly meat. It has also been shown by several investigators that a retention of nitrogen occurs during a period of training—apparently for the manufacture of muscular tissue.

Such views are in harmony with modern conceptions of protein metabolism (p. 545). Since catabolism and synthesis may go hand in hand the total quantity of nitrogen excreted gives no indication of the interchanges which are taking place between food and tissue nitrogen. It is scarcely reasonable to assume that after deamination the non-protein portions of the amino acids can not serve as a source of oxidative energy.

A carnivorous animal, for example, can subsist upon diet composed almost exclusively of protein. Canzulli and Rapport also draw attention to the irrelevance of the nitrogen excretion and insist that it can give no information respecting the non-nitrogenous part of the catabolized protein. From a study of the respiratory quotient of the excess metabolism of exercise performed by a dog on a high protein diet, they conclude that the oxidative energy for muscular exercise can be supplied quite as readily by protein as by carbohydrate or fat.

The question whether or not *alcohol* can furnish energy for muscular work has been investigated by a number of workers. The evidence has been conflicting. Some have reported that muscular exercise hastened the disappearance of alcohol from the blood, presumably by increasing combustion (see Mellanby). On the other hand, Carpenter and his associates in a recent careful study did not find that work exerted such an effect. They conclude that alcohol disappears from the human body at a uniform rate whether the subject is at rest or performing muscular exercise. Nor did muscular work alter the concentration of alcohol in the expired air (i.e. the amount eliminated per liter of CO_2 remained unchanged), in the urine or in the blood.

CHAPTER LIV

THE BODY TEMPERATURE. HEAT BALANCE

The temperature of the body in health as determined from a thermometer placed in the mouth is around 98.6°F. (37.0°C.). The rectal temperature is about a degree higher and the axillary about a degree lower than the mouth temperature. Some persons habitually have a body temperature a few tenths of a degree higher or lower than these figures. Variations in the body temperature also occur in the same individual throughout the day—a difference of 0.5° or even 1.0°F. occurring between the maximum in the late afternoon or early evening, and the minimum at about 4 or 5 o'clock in the morning. In night workers the times of the maximum and minimum temperatures may be reversed. The temperature of the internal organs is higher by 2° or 3°F. than the temperature of the skin. The temperature of the liver, for example, is about 100°F. whereas that of the skin covered with clothes is from 75° to 93°F. The temperature of the bare skin varies widely, of course, with the environmental temperature. The influence of the latter upon the temperature of the covered skin will depend upon the heat-insulating properties of the clothing, air movement (breeze, wind), atmospheric moisture, etc. Strenuous muscular exercise causes a temporary rise in body temperature of from 1.0° to 4.0°F. or more; a temperature of over 104°F. during exercise has been reported (L. Hill).

The heat regulating mechanisms are not fully developed at birth. The body temperature of the newborn child, though in general the same as that of the adult tends to be irregular and unstable. Spontaneous variations of from 1 to 2 degrees are common during the first year.

THE REGULATION OF BODY TEMPERATURE

Mammals and birds possess efficient mechanisms for maintaining a constant body temperature against extreme changes in environmental temperature. It is a remarkable fact that the temperature of a warm-blooded (homoiothermic) animal remains practically unchanged though the surrounding temperature may vary between 0°F. or less and 100°F. or upwards. On the contrary, the body temperature of a cold-blooded (poikilothermic) animal such as the frog, turtle, etc. is practically that of its environment (fig. 243).

The body temperature of the homoiothermic animal represents the balance struck by the heat

produced in the tissues (and heat acquired in warmed food) and the heat lost to the environment. Heat production is the result of chemical reactions and is therefore spoken of as the *chemical regulation* of body temperature. Heat loss is dependent upon physical (and physiological) factors—*physical regulation*.

PHYSICAL REGULATION—HEAT LOSS

Heat is lost from the body through

- (a) *Radiation, convection and conduction.*
- (b) *Evaporation of water from the lungs and skin.*
- (c) *Raising the inspired air to body temperature.*
- (d) *Urine and feces.*

Under the ordinary conditions of every day life over 95 per cent of the total heat loss occurs through (a) and (b). The heat lost in raising the temperature of the inspired air to body temperature (c) will, of course, vary with the air temperature, but at ordinary room temperatures it does not amount to more than 2 or 3 per cent of the total. The air is a very poor conductor, so in terrestrial animals conduction plays a very minor rôle except under special circumstances, as when the body is in contact with a cool object. Radiation is responsible for about 55 per cent of the total heat loss and convection for 15 per cent (see Table below). The heat lost in the urine and feces accounts for only 1 per cent or less of the total heat loss.

The total quantity of heat lost in twenty-four hours must, of course, just equal the amount produced; otherwise the body temperature would rise or fall. The heat production of an average man doing light work is about 3,000 Calories. The proportions of this which are dissipated through the various channels at ordinary room temperature are given in the following table, in approximate figures.

	Calories	Per cent
(a) Radiation, convection and conduction.....	2100	70
(b) Evaporation from skin and lungs.....	810	27
(c) Warming inspired air	60	2
(d) Urine and feces (i.e., heat of these excreta over that of the food).	30	1
Total daily heat loss..	3000	100

Radiation, convection and conduction

The loss of heat by these means varies with (a) the air temperature and other environmental conditions, e.g., humidity and air movement, (b) the nature and amount of clothing, and (c) the quantity of heat produced within the body, i.e., with the metabolism.

The rate of cooling of any warm object varies with the temperature of the air and of colder objects in contact with or near it. When a large temperature difference exists between the two, the warm object loses heat rapidly through radiation, conduction and convection, the rate of heat loss, however, becoming gradually less as the temperature of the object approaches that of the environ-

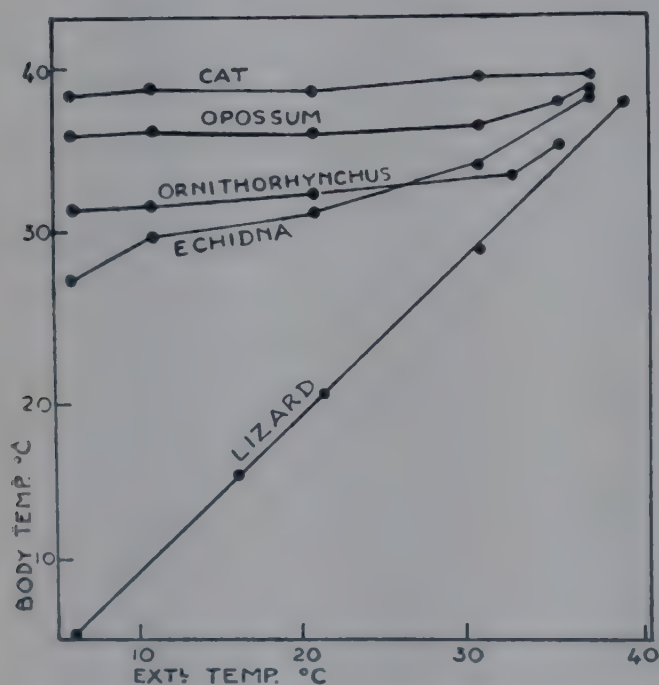


FIG. 243. Variation of body temperature of different types of animals by sojourn for two hours in an environment of 5° to 35°C. (After Martin.)

ment. The dead body behaves in a manner similar to that of any inanimate object, taking from ten to twenty hours on an average to reach the temperature of its surroundings. In the living body, on the other hand, factors operate to encourage or minimize heat loss, respectively, when the environmental temperature is high or low, or corresponding changes in the body's heat production occur. The factors involved in heat conservation or heat loss are dependent essentially upon reactions of the autonomic nervous system. The following are the principle adjustments which take place in the blood-vascular system. (a) *Redistribution of blood.* The cutaneous vessels dilate or constrict and through the diversion of blood from internal regions of the body to the surface, or from the surface to the internal organs, heat loss is increased or diminished, respectively.

At a temperature of 34°C. the quantity of blood circulating through the skin may, according to DuBois, amount to 12 per cent of the cardiac output. These changes may be initiated in one or a number of four ways, a change in temperature of the blood supplying the nervous centers; reflexly through centers in the brain and cord in response to change in skin temperature (stimulation of hot or cold spots, p. 798); through axon reflexes, and finally through responses of the vessels to direct stimulation by changes in external temperature. (b) *Variations in blood volume* (see p. 20). A rise in temperature causes an increase in blood volume; the blood is diluted by fluid drawn into the circulation from the tissues, chiefly the skin, muscle and liver. Blood is expelled from the spleen (p. 53). At low temperatures the blood volume is reduced, the blood becoming more concentrated, as shown by an increase in the percentage of blood solids. These changes in blood volume are of paramount importance in the regulation of body temperature. Barbour has shown that when a dog whose spinal cord has been sectioned in the lower cervical region, is immersed in a cold bath, concentration of its blood does not occur and its temperature falls. When a normal animal is exposed to cold in a similar manner, concentration of the blood occurs and the body temperature remains practically unchanged (fig. 244). (c) *Increased circulation rate* (p. 225).

The epidermis and the subcutaneous tissue when the vessels are constricted are a little more efficient as insulating material than a layer of cork of the same thickness (DuBois). The subcutaneous layer varies considerably in thickness in different persons and is thicker in women than in men. This accounts largely, no doubt, for the greater resistance of the former to low temperatures. For the same reason persons who are overweight, owing to the better insulation provided by the excess subcutaneous fat, are better able to withstand the cold than lean persons, but they also become more easily overheated when, as in muscular exercise, heat production is increased.

Convection, i.e., the rate of movement of warm air from the neighborhood of a heated object varies, of course, with the temperature of the atmosphere. The clothed body has a layer of warm moist air in contact with the skin which tends to become trapped in this situation and in the spaces of the clothing. In the absence of a temperature difference between it and the external air or of some movement to cause mixing, this air will remain practically stagnant. However, when the

atmosphere is cooler, convection currents are set up which mix the air lying against the skin with fresh air. Convection is essentially dependent upon the relative densities of airs at different temperatures, the warmer and lighter air rising, the cooler air falling. Dry air is denser than air possessing a high content of water vapor. One would expect therefore that changes in the humidity of the atmosphere should alter the heat lost by convection but, as a matter of fact, the relative hu-

nearly all infra-red¹ rays (up to 1 or 2 per cent) or absorbs to the same extent all rays which fall upon it (Hardy and Muschenheim). The radiating surface of the human body is only about 85 per cent of the total surface area, since skin surfaces such as in the axillae and between the legs which face one another or are actually in contact do not radiate heat to the environment. The main factor influencing heat loss through radiation is the temperature of surrounding objects relative to that of the skin. The body, for example, radiates heat to a block of ice but absorbs heat from a hot stove or radiator. It should be remembered that the air intervening between the body and the source of heat is not heated by radiant energy, but only by convection. Another factor, though a very minor one, is the humidity of the atmosphere. Air with a high water vapor content is more opaque to radiant heat than dry air. Heat lost through radiation is therefore slightly reduced when the relative humidity is high.

Evaporation of water

It is obvious that the nearer the temperature of the environment comes to that of the blood the smaller will be the amount of heat which can be lost by radiation and convection. At an air temperature of about 98.6°F. heat loss by these means must cease. At higher air temperatures than this, the body, were no other means of cooling available, would actually gain heat. Through the secretion and evaporation of sweat and the exhalation of water vapor (expired air is practically saturated with moisture) large quantities of heat are lost to the body. Its temperature can, for this reason, be maintained constant when the atmosphere (dry) has a temperature about 150°F. above that of the blood (see p. 626). The heat absorbed in the evaporation of 1 cc. of sweat amounts to 0.59 Calorie. Even at ordinary room temperatures when there is no obvious perspiration the heat lost through evaporation from the lungs and skin amounts to from 22 to 27 per cent of the total heat loss. At higher temperatures the increase in the proportion of heat lost by evaporation of water as compared with that lost by radiation and convection is shown in figure 245. It will be seen that evaporation plays little part in heat regulation until the air temperature reaches between 28° and 30°C., the heat loss by this means remaining nearly constant below this level but increasing rapidly

¹ The wave-length of the infra-red rays emitted by skin at usual temperature (34°C.) is 9440 mμ.



FIG. 244. Effects of cool (20°C.) bath upon dog with and without nervous heat regulation. Upper two curves, normal dog; lower two curves, dog after section of sixth cervical cord segment; continuous lines temperature; broken lines, blood solids. Note that normal dog keeps its temperature from falling by means of blood concentration. Dog with sectioned cord is poikilothermic because blood-concentrating mechanism has broken down. (After Barbour.)

umidity of the external air has little effect upon heat loss through convection. Probably the most important factor influencing heat loss by this means is air movement. A breeze or wind greatly increases heat loss by convection up to a wind velocity of around 70 miles an hour. A rise in wind velocity above this has little further effect.

More than half the total heat loss is brought about through radiation (p. 623). The human skin (of whatever color) is an almost perfect "black body radiator." That is to say, it radiates

above it. At a temperature above 35°C. evaporation accounts for all or nearly all the heat lost from the body.

It is to be remembered that evaporation from the body surface occurs quite independently of sweat secretion, for the skin is not entirely impervious to water; fluid extravasated from the cutaneous capillaries seeps into the epidermis. It has been shown for persons in whom sweat glands were absent from birth that some 18 grams of water per square meter of body surface may be lost hourly by evaporation. This is about the same as that of

inversely by the degree to which the atmosphere is already saturated with moisture, i.e., by its relative humidity.² Sweat which is not evaporated but simply drips from the skin, of course does not increase heat loss. For this reason the sweating mechanism for the elimination of heat is badly crippled when the relative humidity is high.³ We are all familiar with the fact that one feels hotter and suffers more discomfort when the atmosphere is hot, and humid ("muggy" or "sticky") than when it is simply hot and dry. A man can maintain a normal temperature in an atmosphere of from 240° to 260°F. provided the air is perfectly dry; the ability to sweat profusely is sustained by large draughts of water and evaporation is facilitated by stripping the greater part of the body's surface. This temperature will actually grill a beefsteak. On the other hand, a damp atmosphere with a temperature of 120°F. causes the body temperature to rise rapidly, and cannot be endured for more than a few minutes. Evaporation and consequently heat loss by this means is greatly hastened by air movement. The layer of air near y saturated with water vapor lying next the skin is thus replaced by drier air.

SWEATING

Sweat is a weak solution of sodium chloride in water together with urea and small quantities of potassium and lactic acid. It has a specific gravity of from 1.002 to 1.003. Its pH as reported by different observers varies from 4.2 to 7.5. The percentage of sodium chloride varies between 0.2 and 0.5. Muscular exercise increases the salt concentration, which is also higher in sweat secreted by clothed than by naked skin. The quantity of non-protein nitrogen ordinarily excreted in the sweat, per day, is according to Benedict 0.071 gram; on the other hand, if the sweating is copious from 0.5 to 1.0 gram may be eliminated per hour. The actual concentration of nitrogen in the sweat falls, however, when sweating becomes profuse, whereas the concentrations of sodium chloride and

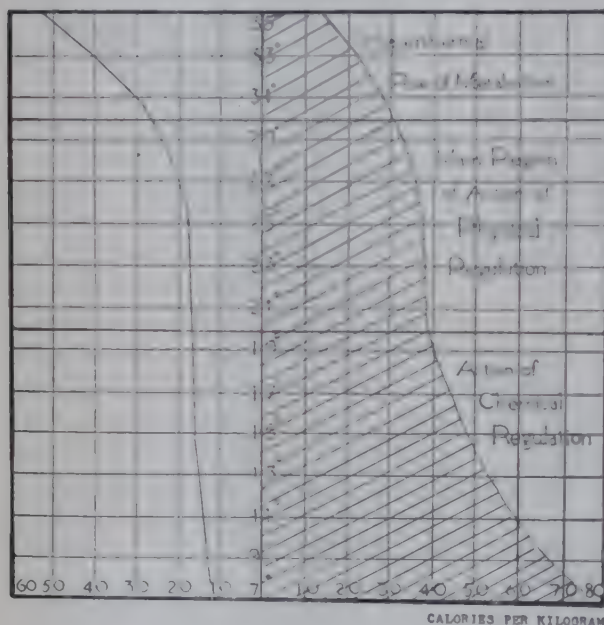


FIG. 245. Rubner's chart showing the manner of heat loss in the dog at different room temperatures. Stippled area, heat loss in calories through evaporation of water; cross-hatched area, heat loss in calories through radiation and convection. The distance between opposite points on the curved lines represents the total heat production at a particular temperature. (Redrawn and slightly modified from Lusk.)

a normal man under ordinary conditions, and represents a total daily heat loss of about 450 Calories for a body of average size (surface area 1.8 square meters).

The respirations are increased by a rise in air temperature or by a greater heat production; the heat loss through warming the inspired air and the vaporization of water from the lungs is thereby increased. Hyperpnea (panting) is the chief means possessed by the dog (in which sweating is practically confined to the foot-pads) for increasing the vaporization of water and combating a rise in body temperature.

The rate of the evaporation of water is influenced

² It is dependent essentially upon the difference in the vapor pressure at the skin and of the surrounding air.

³ The relative humidity is defined as the ratio of the weight of water vapor contained in a given volume of air to the weight which the same volume of air would contain when saturated. The quantity of water vapor which air can hold when saturated increases with the temperature. The relative humidity is expressed as a percentage. Thus, if a sample of air at a certain temperature contains 20 per cent of the water vapor which it is possible for it to contain at that temperature, it is 20 per cent saturated, and so has a relative humidity of 20 per cent.

potassium rise. Therefore, if strenuous work is performed for a long period in a high temperature, and large quantities of water are drunk, depletion of the body's supplies of chloride and a lowered concentration of this element in blood and tissue fluids result.⁴ Severe cramps occur in the muscles of the limbs and abdominal wall ("stoker's" or "miner's cramp"). In order to prevent these effects it is recommended that the thirst be quenched with a weak salt solution (0.2 per cent) instead of with water.

The control of sweat secretion

The sweat glands are under the control of the sympathetic nervous system. These glands are, however, anomalous in their responses to sympathetic and parasympathetic drugs, in that they are stimulated by muscarine, pilocarpine and acetylcholine, and inhibited by atropine (p. 948). According to Coon and Rothman, the action of acetylcholine is twofold,—stimulation of the glands directly through a nicotine-like action and through the initiation of axon reflexes (muscarine-like action). In man and most animals, they are not excited by adrenaline nor paralyzed by ergotoxine. The usual stimulus to sweat secretion is a rise in blood temperature which exerts its effect in two ways—directly upon the nervous centers, which is of more importance, and reflexly by stimulation of heat receptors in the skin. The sweat response to a rise in temperature is abolished by sectioning the nerves to a part and is therefore not due to direct stimulation of the glands. That a rise in temperature of the centers alone will induce the secretion of sweat has been shown by heating the carotid blood in the cat (whose sweat glands are confined to the paw pads); sweating then occurs though the paws themselves remain cool. The centers may also be stimulated in man by the injection of pituitrin into the lateral ventricle (p. 735). In the initial stages of muscular exercise sweating is apparently due to the discharge of impulses from the motor cortex. It occurs before there is any change in rectal temperature. Later on, the effect of a rise in body temperature comes into play. In a man (indoor clothing) at rest, visible sweating usually commences at an air temperature between 80° and 90°F. Sweating may be induced by the experimental stimulation of regions of the diencephalon (hypothalamus, p. 883). Spinal centers also exist, since after complete transection of the cord reflex sweating occurs in the

parts of the body below the level of the lesion (p. 871). Destruction of the sympathetic nerve supply to a part completely abolishes the sweating response to a rise in temperature. The sweat glands, however, still respond to pilocarpine. This drug, which has been employed in the past for the purpose of demarcating areas deprived of their sympathetic supply, is of no diagnostic value, for it acts peripherally, i.e., directly upon the gland cells. Sweating is not dependent upon the circulation for it occurs after occlusion of the vessels and can even be induced by stimulation of the nerves in an amputated limb. Though usually associated with cutaneous vasodilation it may occur with constricted vessels—*cold sweat*. This is usually the result of psychic influences, e.g., nervousness, fear, fatigue or mental work. The sweating occurs in these instances most noticeably on the forehead, the palms of the hands and the soles of the feet. In many persons reflex sweating, confined to the face, is induced by eating spicy food (gustatory sweating). Faradic stimulation of the human skin over the forearm induces local sweating due apparently to direct stimulation of the glands, for it occurs after section and degeneration of the nerve supply.

The few observations that have been made upon the secretion pressure of sweat indicate that it is high—250 mm. of mercury or more. Sweat is therefore a true secretion and not simply a filtrate. The secretion rate may be enormous, amounting to a liter or more per hour, and may be increased some 80 times over the normal by immersing the body in a bath at 108°F. At ordinary room temperatures the sweat evaporates as quickly as formed, so that there is no apparent secretion. The loss of sweat in this way together with the evaporation of water from the lungs and from the surface of the body independently of the sweat glands is called *insensible perspiration*. Its amount varies directly with the basal metabolism.

THE CHEMICAL REGULATION OF BODY TEMPERATURE—HEAT PRODUCTION

The several factors which stimulate the chemical processes of the body and so increase the heat production (metabolism) have been dealt with in Chapter XLVI. There remains to be given an account of the manner in which chemical and physical factors interact to maintain a constant body temperature.

A low environmental temperature is a potent influence in stimulating heat production. At air temperatures below about 28°C. the body (nude) loses heat rapidly. Within the temperature

⁴ A miner performing heavy work may lose a quart of sweat per hour.

range between 28° and 30° or 31°C. the naked male body is able quite easily to maintain the balance between heat loss and heat production. There is neither sweating nor shivering and a male subject feels comfortable. This range of temperature is therefore called the *comfort zone*. For reasons given below the comfort zone is broader (27° to 32° or 33°C.) for women. The external temperature below which heat production must be increased in order to maintain a normal body temperature is sometimes called the *critical temperature*.

Below the critical temperature radiation of heat from the body increases progressively with falling air temperature, but heat loss by conduction and vaporization shows little change. The naked body at a temperature below the critical level loses more heat than it can produce in the basal state, and at about 23°C., or when the body temperature has dropped by about 0.6°C., a chill (shivering) occurs. Heat production is thus increased in an effort to raise the body temperature to the normal level. In the human subject heat production is not increased until the onset of the chill and in men under basal conditions the metabolism remains constant within the range of air temperature from 35° to 22° or 23°C.⁵ It has been shown by Hardy and DuBois that this is not true for women. They show a *reduced* heat production of from 14 to 20 per cent at temperatures between 30° and 32°C. Also, owing to the greater insulation afforded by the thicker layer of subcutaneous fat the heat loss of the female body in a cold environment is some 10 per cent less than that of men. Thus women have a more efficient thermo-regulating mechanism than have men, being better able, contrary to general belief, to resist cold and also to be more comfortable at higher temperatures. The temperature of the female skin is more than 1.5°C. higher than that of a man's skin at the higher environmental temperatures; a woman also sweats less. In a cold environment a woman's skin is about 1.0° cooler than a man's since the conduction of heat from deeper parts is impeded by the thick mantle of subcutaneous fat.

The critical temperature and the temperature of comfort will vary of course with the amount and nature of the clothing. The cooling effect of water is some 14 times greater than that of air—a cold

bath at 40°F. increasing the heat production some 12 times above the resting level for the first minutes or so⁶ (L. Hill and Campbell); after that the heat-producing mechanism becomes depressed and the body temperature falls.

It will be seen from figure 246 that heat loss increases both above and below the critical temperature. At the lower temperatures heat is lost mainly by radiation and convection, at the high temperatures mainly by vaporization. It will also be noticed that at the lower temperatures the skin temperatures follow a straight line, but that the curve commences to flatten out at about 30°C. This is attributed to dilatation of the c

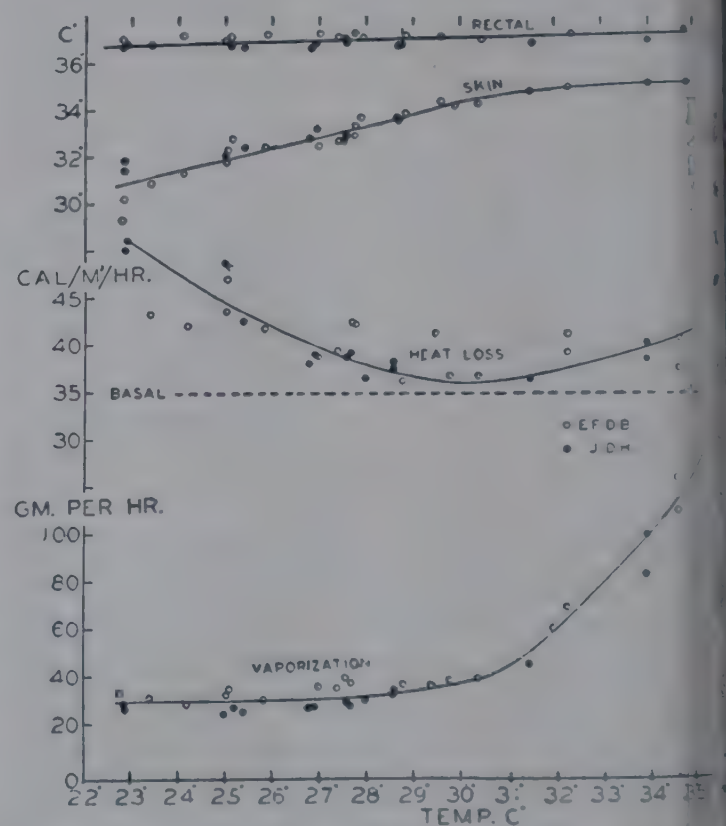


FIG. 246. Showing effect of a rising air temperature on rectal and skin temperatures, heat loss, and vaporization. (Modified from DuBois.)

taneous vessels and the flooding of the skin with blood.

The muscular tissues (particularly of the extremities) and the liver wherein numerous chemical reactions are carried out, are the main sources of the body's heat. The rise in metabolism which results from a fall in atmospheric temperature is effected through an increase in tone of the skeletal muscles and in some instances by fine involuntary contractions, e.g., shivering and chattering of the teeth. Contractions of the smooth muscle of the skin, giving rise to "goose flesh" also contribute. In some mammals and in birds, the contraction of

⁵ Rubner believed that chemical regulation at low environmental temperature involved some factor other than an obvious increase of muscular activity. In animals, adrenaline is liberated during short exposures to cold and stimulation of the thyroid by prolonged periods has been demonstrated (p. 630), but chemical regulation of this nature has not been shown for man.

⁶ In cold-blooded animals, which possess no chemical regulation, the metabolism as measured by the carbon dioxide output falls with the environmental temperature.

the cutaneous muscles also curtails heat loss through ruffling of the hair or feathers. When the skeletal muscles are paralyzed by curare, the animal loses the power to maintain a normal body temperature in a cold environment. Its physical mechanisms of control are, however, intact so that it can resist high air temperatures. Isolation of the muscles from control by section of the cord in the lower cervical region (C.6) also abolishes the chemical regulation. This operation abolishes physical regulation as well, for, as already mentioned, concentration of the blood does not occur and the body temperature falls when the animal is exposed to a low temperature (fig. 244). The rise in body temperature mentioned on p. 623 as occurring in strenuous muscular effort is apparently due, not to any failure of the heat-dissipating mechanisms, but to the "thermostatic" control being set at a higher level, for the temperature

TABLE 63

ATMOSPHERIC TEMPERATURE	HEAT PRODUCTION CALORIES PER KILOGRAM BODY WEIGHT		
	Starved	550 grams of meat fed	Increase
°C.			
4.2	128	133	4
14.5	101	111	9
22.1	71	101	43
30.7	62	117	89

rise is the same whether the exercise is performed at an air temperature of 3° or of 23°C.

Food, especially protein through its *specific dynamic action*, is an important factor in the chemical regulation of body temperature. At high environmental temperatures the specific dynamic action of food acts counter to the physical mechanisms which hasten heat loss. For this reason a low protein diet is more suitable in hot weather. At very low atmospheric temperatures, on the contrary, the specific dynamic effect of food is almost completely masked, since it simply replaces the environmental effect (cold) upon heat production. That is to say, the neuromuscular mechanisms called into play to increase heat production at low temperature are less necessary since the food itself stimulates the body cells to a higher level of metabolism. Protein food in cold climates is therefore a valuable aid to the chemical regulation of body temperature.

The effect of protein ingestion upon the heat production of a dog at different temperatures is shown in table 63 (Lusk).

CONTROLLING CENTERS

Section of the neuraxis through the mid-brain at the level of the superior colliculi or at any level posterior to this and anterior to the lower cervical cord renders an animal poikilothermic (fig. 247). Section of the cord in the upper thoracic region, i.e., above the level of the outflow of the greater part of the sympathetic fibers, abolishes physical heat regulation but leaves chemical regulation to a large extent intact, since the muscles of the fore part of the body remain in communication with the central nervous system. The effect of section through the brain stem indicates that the main center or centers controlling heat regulation must lie anterior to the superior colliculi. Removal of the cerebral cortex, thalamus or corpus striatum does not destroy the controlling mechanisms so long as the hypothalamus remains intact. Destruction of this region alone, however, was found by Keller and Hare to abolish the ability to maintain a normal body temperature upon exposure to cold. The heat-dissipating mechanisms remained intact and were, in fact, released from restraint by the hypothalamic lesion, as evidenced by pronounced panting and vasodilatation.

The thermoregulatory centers have been located more precisely by Ranson and his associates. From the results of their experiments upon cats and monkeys they place the centers controlling heat loss (sweating and panting) in the preoptic and supraoptic regions between the anterior commissure and the optic chiasma. Heating this area causes sweating and panting or rapid breathing, and a fall in body temperature. Destructive lesions in this situation are followed by hyperthermia when the animal is exposed to a degree of heat that would cause little effect upon the body temperature of a normal animal. Sweating or panting does not occur though the temperature rises to over 106°F. Such lesions have little effect upon the animal's ability to resist cold. The centers controlling heat production and heat conservation, i.e., the mechanism whereby an animal is enabled to maintain a normal body temperature when exposed to cold, is situated, according to these investigators, in the caudal part of the lateral hypothalamus; it appears to be identical with the sympathetic center. The existence of a center for shivering (heat production) in the hypothalamus is suggested by the fact that under certain circumstances shivering in animals is accompanied by some of the manifestations of "sham rage" (Barcroft and Izquierdo). That the posterior part

of the hypothalamus contains the main shivering center is indicated by the experimental results of Kellar and his associates and of Ranson and his colleagues who found that, in cats, shivering was abolished by a destructive lesion in this situation. The efferent pathway for shivering is unknown, but an observation upon a patient in whom both spinothalamic tracts had been sectioned and who did not shiver when the legs were immersed in cold water, suggests that the impulses descend the cord

uncommonly with hyperthermia; hypothermia, on the other hand, may accompany lesions involving the posterior part of the hypothalamus.

As mentioned on page 624 the main heat-regulating centers are apparently influenced in various ways—reflexly from the skin and by the temperature of the blood flowing through them.

The posterior hypothalamic center apparently exerts its controlling influence upon temperature through the transmission of sympathetic impulses to the cutaneous vessels, sweat glands and peripheral motor muscles; removal of the sympathetic innervation renders an animal unduly susceptible to cold (p. 945).

THE ENDOCRINES IN THERMOREGULATION

The thyroid and adrenals also play their probably important roles in the regulation of body temperature. The calorogenic effects of the secretions of these glands are well known (pp. 682, 683). Cannon observed that exposure to cold caused an increase in the rate of the denervated heart (p. 690). It has also been reported that the serum taken from an animal exposed to cold raises the metabolism of a second animal into which it is injected. If the first animal has been thyroidectomized, the effect upon the metabolism of the second is not observed. The adrenal secretion exerts a calorogenic effect which is immediate and of short duration. Its liberation follows short periods of exposure to cold. But owing to the delayed action of the thyroid hormone and the persistence of its effects it does not seem possible that the thyroid could play any part in increasing heat production unless the cold stimulus were continued over a long period. Rats exposed over a period of weeks to low temperatures (7.8 to 12.2°C) showed thyroid hyperplasia and a rise in metabolic rate of as much as 16 per cent which was not reached, however, until the lapse of from 2 to 3 weeks. Thyroidectomized rats, on the contrary, show little rise in metabolic rate under the same conditions. The experiments of Uotila point to the pituitary as being responsible for the thyroid response to cold, for hypophysectomy causes thyroid atrophy as usual, though the animals are exposed to a low temperature for long periods. It may be mentioned in this connection that the temperature tends to be subnormal in suprarenalectomized or thyroidectomized animals, in Addison's disease, and in cretinism.

DISTURBANCES OF HEAT REGULATION

Since the body temperature represents the balance struck between heat production and heat loss

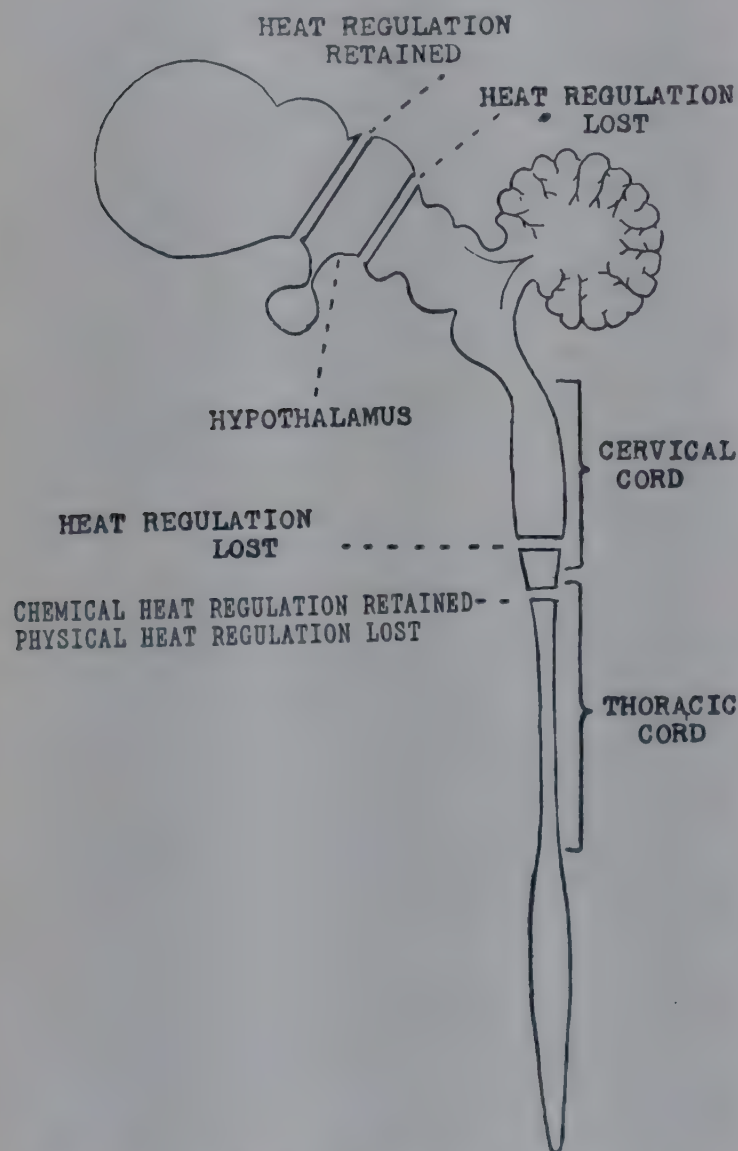


FIG. 247. Diagram to illustrate the nervous control of the heat-regulating mechanisms. (Modified from Martin.)

by these paths. The impulses are not transmitted by sympathetic nerves, since shivering occurs in sympathectomized parts. Shivering is reduced or abolished by certain drugs, especially calcium chloride and aminopyrine which act most probably upon the shivering center.

From observations of patients with intracranial lesions involving the base of the brain, it seems most likely that in man the centers are situated as described by Ranson and his associates for animals. Lesions in the supraoptic region are associated not

a disturbance in the value of one of these factors in relation to the other obviously will be followed by a temperature change.

Temporary rises in temperature may occur in health as a result of hot baths which prevent heat loss through conduction, radiation and the evaporation of sweat, as well as by actually adding heat to the body; or during violent muscular exercise which increases heat production. Owing to the high efficiency of the chemical mechanism of control, a fall in the temperature of a normal person is much more difficult to produce than is a rise.

The heat regulating mechanisms are depressed by anesthetics, during sleep and hypnosis and by general bodily fatigue.

HEAT STROKE

Heat stroke is due to exhaustion or inadequacy of the heat dissipating mechanisms and occurs as a result of exposure to a hot humid atmosphere; the hyperthermia may seriously damage the nervous tissues and prove fatal. *Sunstroke* is simply a form of heat stroke; but in addition to the reduction in heat loss as a result of the high atmospheric temperature there is an absorption of solar radiant energy. This may cause a local elevation of temperature above that of the body generally in regions such as the brain or cervical cord, which are unprotected from the heating effects of the sun's rays. Powerful sunshine itself, however, will not cause sunstroke provided heat dissipation is adequate to keep pace with heat production, i.e., when the air is dry and cool and strenuous exercise is not undertaken. The most valuable measures for the prevention of these effects of overheating are, a light diet, avoidance of exertion, plenty of water to drink, loose airy clothing or stripping to the waist, electric fans, cold douches and the protection of the head and nape of the neck from the direct rays of the sun.

FEVER (PYREXIA)

Types of fever:

- (1) *Infectious fever*, e.g., sepsis, typhoid, pneumonia, etc.
- (2) *Surgical fever* which arises after an extensive aseptic operation and is apparently due to toxic substances liberated by the injured tissues.
- (3) *Neurogenic fever* from injuries to nervous centers, especially lesions in the neighborhood of the third ventricle, internal capsule, medulla or upper part of spinal cord.
- (4) *Fever of dehydration* due to a reduction of blood-water (anhydremia, p. 19). This is particularly likely to occur in young children.
- (5) *Fever produced by drugs and other chemical substances.*

Intravenous injections of concentrated *solutions of glucose* or *salt* induce fever by causing anhydremia (p. 19). Drastic *cathartics*, by drawing water from the blood into the bowel, may cause fever in a similar manner. *Caffeine* and *cocaine* in large doses induce fever by increasing muscular tone (greater heat production) and by causing blood concentration (reduced heat loss, see also (p. 624). *Hemoglobin* solutions when injected into the blood stream exert a pyretic action; the hemolysis resulting from the intravenous injection of distilled water acts similarly. The manner in which the fever is produced is unknown. *Beta-tetrahydronaphthylamine* injected subcutaneously raises the temperature by its action upon the central and peripheral sympathetic mechanisms, causing cutaneous vasoconstriction and consequently a greater conservation of heat. It also, through its action upon the muscles, causes increased heat production. The adrenal medulla is also probably stimulated by this drug and the outpouring of adrenaline may be an added factor in the temperature rise. *Ergotoxine* causes a rise in temperature in some animals (cat), presumably through a direct action upon the heat centers. *Dinitrophenol*, a drug sometimes used in the treatment of obesity (p. 611), and injections of *foreign protein* also raise the body temperature. Dinitrophenol acts by stimulating oxidative processes in the tissues. *Adrenaline* and *thyroxine* in large doses may also, through their stimulating effect upon the metabolism, cause a rise in temperature.

Infectious fevers

At the *onset* of an acute infectious fever the heat balance is upset by a reduction in heat loss as a result of vasoconstriction and a reduction in blood volume, combined with an increase in heat production. That is, those mechanisms which in health prevent a fall in temperature when the body is exposed to cold, are called into play by a stimulus within the body itself, namely, the toxin of the infecting organism.

The reduced heat loss by radiation and convection in the early stages of the fever is evident in the cold, pale or slightly cyanosed skin. At this time, though the body temperature may be higher than at any subsequent stage, the patient often experiences sensations of extreme cold (chills) with shivering, chattering of the teeth and "goose flesh." In health, the comfortable feeling of warmth depends not upon the temperature of the deeper structures but upon the stimulation of the cutaneous sense organs (corpuncles of Ruffini) by the warm blood coursing through the superficial vessels. The chills are due to the spasm of these vessels and the exclusion from them of the warm blood of deeper regions. The fall in skin

temperature acts as a stimulus which calls into play the mechanism of chemical regulation; shivering, which consists of fine contractions of the muscles, occurs; muscle tone increases; and the smooth muscle of the skin contracts. The increased heat production thereby induced is an additional factor in the elevation of the body temperature. Later, when the body temperature reaches a certain height, a heat response is evoked from the centers, the vessels are released from spasm, the blood flow through the skin increases, the body surface becomes flushed, and the patient feels intensely hot. The balance between heat loss and heat production is again restored but set at a higher level than in health. The body's "thermostat" is turned up a point or so.

DuBois in an experiment upon a normal man and a malarial fever patient demonstrated the reduced heat elimination which occurs during the chill. The normal subject imitated as closely as possible for a period of 34 minutes the shivering of the patient and thereby increased his heat production by nearly 200 per cent. Most of the extra heat was eliminated as it was produced, the body temperature showing only a slight rise. In the malarial patient, on the contrary, in whom the heat production during the chill was increased to about the same degree, all the extra heat was retained.⁷ The heat retention caused a rise of 2°C. in body temperature. After the chill the heat elimination rose and the temperature fell.

The *continued* fever which usually follows the initial chill of an infectious disease, or which develops in other instances without this preliminary, is due essentially to the raised threshold for heat loss. There is, of course, increased heat production but this is mainly secondary—the velocity of the oxidative processes of the tissues being increased by the rise in temperature induced by the diminished heat elimination.⁸ That the latter rather than increased heat production is the principal factor in the elevated temperature is indicated by the fact that in fever a temperature of 104°F. (40°C.) is accompanied by an increased heat pro-

duction of only about 35 per cent whereas in health the heat production must be increased several fold (as in muscular exercise) in order to raise the body temperature even transiently to this extent. Although the metabolism may be raised 40 per cent or so in an animal by protein feeding (see specific dynamometer action, p. 554) without the occurrence of a temperature rise. Furthermore, the increased metabolism in ordinary fevers occurs simultaneously with the temperature rise. If the latter were the result rather than the cause of the former, it should be possible to demonstrate by indirect calorimetry a period of increased metabolism *preceding* the rise in temperature; this, however, does not occur.

With the termination of the fever, sweating (or at least moistening and cooling of the skin) occurs, the heat-balance is restored to its normal level, the heat which had been retained is eliminated either

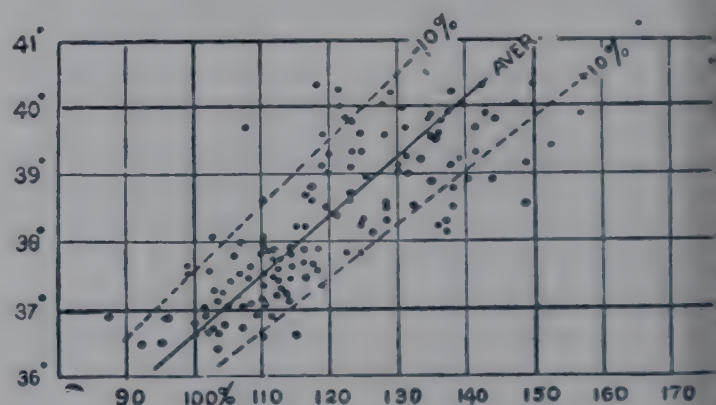


FIG. 248. Shows relationship between basal metabolism and body temperature in fever. Results in six different fevers grouped in one chart. The continued line shows the average metabolism, the interrupted lines the metabolism 10 per cent above and 10 per cent below the average respectively. (After DuBois.)

gradually or with comparative abruptness (crisis) and the temperature falls.

In infectious fevers the bacterial toxins act either directly or indirectly upon the heat center or center. In decerebrate animals or in those in which the cord has been divided in the lower cervical or upper thoracic regions the injection of infective agents does not cause fever nor is a rise in temperature so produced in animals possessing no heat regulating mechanisms. Balfour suggests that the first effect of the toxin is not directly upon the heat regulating centers but upon the peripheral tissues. In these, it is conceived, chemical changes are initiated which result in the withdrawal of water from the blood. The reduced volume of circulating fluid causes blood to be drained from the skin vessels and thereby calls forth a reflex cold response from the heat regulating mechanisms. That is, the nervous centers respond by causing vascular spasm, shivering and a further increase in blood concentration. The mechanism involved at the onset of fever is there-

⁷ The water equivalent of the human body is 0.83 times its weight in kilograms (W) per °C. rise in temperature (t°C.); the retained heat may therefore be calculated from the formula $t^{\circ} \times W \times 0.83$.

⁸ The increase in metabolism with rise in temperature follows van't Hoff's law which states that the velocity of chemical reactions increases from 2 to 3 times for a temperature rise of 10°C. That is, the *temperature coefficient* is between 2 and 3. The basal metabolism actually increases about 13 per cent for each degree Centigrade rise in body temperature or 7 per cent for each degree Fahrenheit (fig. 248).

fore comparable to that which produces a rise in temperature of a healthy man after a cold plunge. The cold water causes, through vasoconstriction, diminished heat dissipation and through shivering, increased heat production. The body temperature may rise for a few minutes. After the first effect of the plunge the vessels are released from spasm, the stored heat is eliminated, the surface of the body glows and a feeling of comfortable warmth is experienced. This constitutes the "healthy reaction" of a cold shower and may be compared to the period following the fever chill, except that in the latter case the heat balance is set at an abnormally high level. The factors causing the continuance of the fever, on the other hand, are similar to those which cause a rise in temperature during the immersion of the body in a hot bath. Heat dissipation is greatly reduced and heat production is increased purely as a result of the elevation in temperature of the tissue cells.

Special metabolism in fever

Water and salt. At the onset of a high fever the blood volume, as already mentioned, is reduced, the reduction being due to the loss of water (anhydremia). Later the volume of the blood tends to increase (hydremlia) as a result of the shift of water from the tissues to the vessels. During the course of the fever the urine volume is markedly reduced, but is increased above the normal when the temperature falls. The vaporization of water is greatly increased in fever, owing chiefly to the high temperature of the skin and lungs.

There occurs a retention of chloride which apparently is deposited in the tissues, the chloride concentration of the blood being normal or below normal. The urinary chlorides in most fevers are greatly reduced. At the termination of the fever the retained water and chloride are eliminated by diuresis and sweating. Chloride retention is especially pronounced in pneumonia.

Protein. The excretion of nitrogen in the urine is greatly increased in most infectious fevers. This is furnished by body protein, the protein minimum, i.e., the "wear and tear" quota of protein metabolism (p. 554), being much higher than normal. In very severe infections from 300 to 400 grams of body protein may be destroyed daily. It has been found impossible to maintain the fever patient in nitrogen equilibrium (p. 552) by giving liver allowances of protein combined with supplies of carbohydrate which under ordinary circumstances would be considered quite adequate for energy purposes. It has, therefore, been held that the toxins of the disease were responsible for the protein destruction, the so-called "*toxic destruction*"

of protein. It has been shown, however, by Shaffer and Coleman that if a diet be given possessing a caloric value 50 to 110 per cent in excess of the patient's requirements, as actually determined by calorimetry, and containing a liberal supply of protein (160 to 200 grams) nitrogen equilibrium *can* be established. The high protein catabolism which has been observed in fever patients on the usual diet is therefore thought to have been due in large measure to the fact that the caloric intake was far below the requirements, which owing to the higher metabolism in fever are considerably greater than has been supposed. In other words, a fever patient upon a diet which has been considered adequate in the past is actually in a half-starved state, and is, in consequence, forced to consume his own tissues.

Nevertheless, even on a high caloric diet composed of carbohydrate and a small quantity of fat, the nitrogen excretion still remains well above that of a normal person. Moreover, a protein allowance equivalent to that of a healthy man together with carbohydrate somewhat more than sufficient to cover the calculated calorie requirements of the febrile state will not maintain nitrogen equilibrium. As just mentioned, the calorie allowance must in some instances be double the heat production of the patient. It therefore appears that the toxic process itself must be responsible in part for the increase in protein metabolism. Creatinine, uric acid, purine bases and phosphates also appear in the urine in increased amounts—further evidence of a destruction of body protein. The manner in which the "toxic" effect is produced is not known, but since it can be abolished by an appropriate diet it is evidently not due to the bacterial products acting directly—simply as protoplasmic poisons. Nor does it appear that the protein destruction is merely the result of the high temperature, for, raising the temperature of a normal person to 104°F. by immersion in a hot bath does not increase the nitrogen excretion significantly.

It must be apparent from the foregoing remarks that in order to reduce the waste of body tissue in fever a liberal diet should be given, provided such is not contraindicated by some special feature of the disease. The old adage "feed a fever" holds true. Since the very high protein diet required for the establishment of nitrogen equilibrium in the fever patient has its disadvantages, one must usually be satisfied with reducing the waste of body protein rather than aiming to abolish it. Special attention, therefore, is directed toward furnishing

an abundance of protein-sparing food (p. 553), namely carbohydrate, and thus avoiding excessive quantities of protein. The more abundant diet causes a negligible increase in heat production and no elevation of the temperature.

Fats and carbohydrates. The metabolism of body fat or carbohydrate shows no definite abnormality in fever. In patients upon a low food intake body fat and glycogen are utilized as fuel. Acidosis results from the incomplete combustion of fat only if the available carbohydrate is inadequate in amount.

THE ACTION OF ANTIPYRETIC (FEVER-REDUCING) DRUGS. A list of chemical substances which are capable of inducing a rise in body temperature has been given on page 631. Other drugs, e.g., antipyrine, aspirin, salicylates, quinine, etc. though they exert little effect upon the normal temperature, lower the temperature in fever by increasing heat elimination. According to Barbour they bring about this effect through drawing water from the tissues into the vessels and thus increasing the volume of fluid in the body's heat radiating system. They appear to exert little effect upon heat production. The effect upon the blood volume is possibly brought about indirectly. All these substances raise the blood sugar; the greater sugar concentration may then through osmotic forces attract water into the vascular system.

Certain other drugs, e.g., morphine, general anesthetics and alcohol, tend to depress the *normal* body temperature chiefly through blood dilution and dilatation of superficial vessels. In the case of morphine and general anesthetics a direct depressant action upon the heat centers is also indicated.

THE VALUE OF FEVER. Fever is frequently the herald of serious disease; nevertheless, unless of high degree and on this account endangering the functions of vital tissues, it should not be looked upon as a reaction detrimental in itself. On the contrary, there is every indication that its occurrence is an important aid to the body in its combat with the disease. The rôle which fever plays in the defensive process is, however, unknown. It was been suggested that the formation of antibodies can be elaborated only at higher

temperatures. It is well known, for instance, that infections which overwhelm the individual the temperature reaction is depressed. In support of the belief that moderate fever is not injurious in itself but actually beneficial the following observations upon animals may be cited. (a) The body temperature of rabbits has been maintained by the application of external heat at a level of over 105°F. for weeks at a time without ill effects. (b) In animals infected with certain microorganisms the disease runs a milder course when the temperature is raised (to 40°C.) artificially. (c) It has been reported that with moderate overheating the formation of various antibodies is increased, but at higher temperatures the process, apparently, is depressed. The immunity of fowl to the ordinary pyogenic infections is ascribed to their higher body temperature which is inimical to the growth of pus-forming bacteria. (d) Fevers induced artificially by means of foreign proteins or injections of malarial blood are used as therapeutic agents in arthritis and certain chronic nervous diseases. Short wave diathermy has been employed with success in the treatment of certain infections—the high temperature produced in the tissues exerting a lethal action upon the microorganisms.

REFRIGERATION—CRYOTHERAPY. In chronic incurable disease e.g., carcinoma, refrigeration of the patient is sometimes resorted to for the relief of severe intractable pain. Ice is packed around the patient or some other means is used to reduce the temperature of the body to between 80° or 90°F. This temperature is maintained for hours or days. The patient becomes unconscious, passing into a state of "suspended animation," which in many respects is comparable to that of an animal during hibernation. The heart rate and respirations are slowed and the radial pulse may be imperceptible. The blood pressure falls below the level at which it can be measured, urine production is greatly diminished or suppressed and gastrointestinal activity is minimal. The blood volume is reduced as a result of the loss of water (hemoconcentration or anhydremia). The metabolism, in accordance with van't Hoff's law is reduced by from 20 to 50 per cent. The respiratory quotient is probably not greatly lowered, but in hibernating animals, in which the metabolic processes are altered qualitatively as well as quantitatively, it is around 0.60.

CHAPTER LV

THE VITAMINS

INTRODUCTION. NOMENCLATURE

In 1911 Casimir Funk, as a result of his investigations into the cause of beri-beri obtained a crystalline substance from rice polishings which was capable of preventing or curing this nervous disease. He named the substance *vitamine* in view of its quite evident importance to life, believing, though erroneously, that it was an amine. Subsequently a number of similar substances playing an essential rôle in nutrition were discovered for which the general term *vitamin* was agreed upon, the individual vitamins being designated by letters of the alphabet. In the state of knowledge at the time such a method of designation had the advantage of being non-committal as to the chemical nature and other properties of this group of substances. The following is a classification of the known vitamins and their chief physiological effects:

Vitamin A (antixerophthalmic)

Vitamin B complex	<div style="display: inline-block; vertical-align: middle;"> <div style="display: inline-block; vertical-align: middle;"> thiamin (B₁) riboflavin (B₂) nicotinic acid pyridoxin (B₆) pantothenic acid inositol biotin para-aminobenzoic acid choline </div> </div>
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Vitamin C (antiscorbutic)

Vitamin D (antirachitic)

Vitamin E (antisterility)

Vitamin K (antihemorrhagic)

Vitamin P (capillary permeability)

Vitamins A, D, E and K are fat-soluble. The others, namely, those of the B complex, C and P are water-soluble. Riboflavine is also called vitamin B₂ and sometimes vitamin G (see p. 642).

VITAMIN A (ANTIXEROPHTHALMIC)

This was discovered as a result of the investigations of Hopkins in England and of Osborne and Mendel, and McCollum and Davis in America.

Sources

The chief sources of vitamin A are mammalian and fish liver, egg yolk, butter, cream and a number

of vegetable foods. Cod-liver oil has a very high but halibut oil a much higher content in this vitamin. Vegetable oils with the exception of corn oil and red palm oil contain little or none. Lard and beef fat are as a rule poor sources of this vitamin; their vitamin A content varies considerably, however, with the animal's diet. Cereals, with the exception of maize, are relatively poor in vitamin A. In plant tissues there is a definite relationship between their green or yellow coloring and their vitamin A activity. Thus, the sweet (yellow) potato is a good source, whereas the ordinary potato possesses very little or none; the outer green leaves of lettuce contain some 30 times more of the vitamin than do the inner white leaves. Carrots, yellow maize, escarole, spinach, cress, string beans, green peas, pumpkin, bananas and cantaloupe are rich in the vitamin whereas in white corn, celery, cauliflower, white turnips, cabbages, radishes and other colorless vegetables it is present in small amounts or entirely lacking. The *vitamin A requirement* for man is from 4000 to 6000 international units (p. 662).

Chemical properties and history in the body

Vitamin A is soluble in fats and fat solvents. It is present in the unsaponifiable fraction of the fat. It is resistant to heat in the absence of air but is readily destroyed by oxidation at all temperatures. Though colorless itself it gives a blue color with antimony trichloride in the presence of oxygen. In oily solution vitamin A, or its esters in alcoholic solution, show a green fluorescence when exposed to ultraviolet light. This property has been employed to demonstrate microscopically its distribution in the body tissues, e.g., Kupffer cells, retina, adrenal cortex, testes and corpus luteum. It is also seen in actively secreting mammary glands and in tumor tissue. The fluorescence gradually fades, presumably as a result of the destruction of the vitamin by the ultraviolet rays.

Vitamin A is an unsaturated alcohol with the empirical formula C₂₀H₃₀O and is derived from the reddish yellow pigment *beta-carotene*—C₄₀H₅₆—one molecule of the latter being split into two molecules of the vitamin, thus; C₄₀H₅₆ + 2H₂O → 2C₂₀H₃₀O.¹

¹ Carotinoid pigments of vegetable food are also largely responsible for the fat pigment of animals.

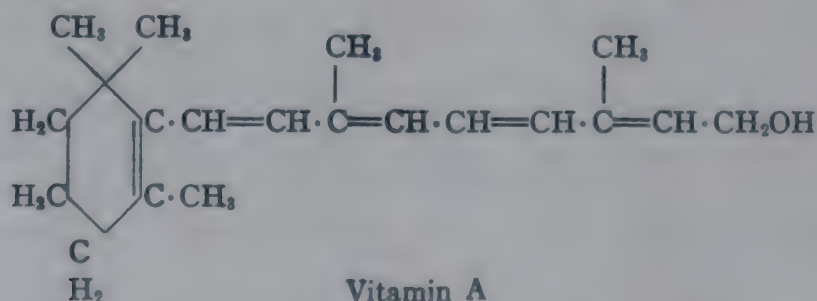
Vitamin A has been isolated in crystalline form and recently synthesized. Euler, in 1928, showed that pure carotene from carrots was capable of replacing vitamin A in the diet. Moore later found that feeding rats with pure carotene caused a great increase in the vitamin A contents of their livers. It is therefore concluded that carotenes, of which there are three forms, *alpha*, *beta* and *gamma*, and possibly other plant pigments (e.g., cryptoxanthin) are the precursors of vitamin A. Beta-carotene is of chief importance; the alpha form gives rise to one molecule only of vitamin A. When taken in the food, the carotene or *provitamin*, as it is called, is converted into vitamin A in the liver where it is also stored (probably in the Kupffer cells). The conversion is relatively slow and not complete; probably not more than from 30 to 50 per cent of ingested carotene is converted into the vitamin. Drummond and McWalter found an increase in the livers of rabbits eight days after the intravenous injection of carotene, but not sooner; incubation of carotene *in vitro* with liver tissue did not, however, result in the formation of vitamin A.

Vitamin A does not, apparently, exist as such in plants but only in the form of the provitamin.² Algae, diatoms and other marine plants synthesize the provitamin, and serve as food for small marine forms referred to in general as zooplankton, i.e., copepods, molluscs, etc. The zooplankton serve as food for various species of small fish (herring, whiting, young cod, etc.) which thus receive the necessary supplies of provitamin. The smaller fish upon which the larger fish such as cod and halibut feed provide these latter with vitamin A. Herbivorous animals obtain the provitamin from fodder (alfalfa is a particularly rich source). Dairy

foods rich in the provitamin or animal tissue which contain it preformed. The concentration of vitamin A in the liver of the new born infant is low for the placenta transmits little from the mother the concentration increases gradually during the first few weeks of life, the vitamin being supplied to the off-spring in the milk. The quantities of vitamin A and carotene in human milk are relatively high, and are highest in colostrum and early milk. Bile, though necessary for the absorption of carotene, is not required for the absorption of vitamin A. Absorption of both the vitamin and provitamin, on the other hand, is favored by the presence of fat or phospholipids, e.g., lecithin, in the intestine, whereas petrolatum has a definitely depressing effect, especially upon the absorption of carotene. The vitamin is found in the liver and intestinal tract, chiefly in the form of esters, which, before their absorption from the latter situation, are hydrolyzed by the lipases of the intestinal and pancreatic juices. During absorption the vitamin is found in the intestinal mucosa in the form of the alcohol.

In experiments upon rats Moore discovered an interesting synergic relationship of vitamin E with vitamin A. The administration of vitamin E increases the storage of vitamin A in the liver, prolongs the time required to exhaust the reserves and postpones the dental abnormalities due to vitamin A deficiency. Vitamin E probably exerts its effect by acting as an antioxidative agent in the gastro-intestinal tract. Rancid fats and unsaturated fatty acid esters (linolenates, linolates) have the opposite effect, tending to inactivate vitamin A through oxidation.

Vitamin A has been given the following structural formula by Karrer.



cattle convert it in part into the colorless vitamin A.³ This, as well as unchanged carotene is excreted in the milk. Man may therefore acquire a supply of this vitamin either by consuming plant

² Since the actual and only important effect of carotene after ingestion is that of vitamin A, it still remains the custom to speak of the vitamin A value of a food rather than of its carotene content.

³ The proportion of carotene converted, and so the color of the milk, varies in different breeds of cattle. It is evident that a pale-colored milk may have a vitamin A value as high as or higher than one more richly colored.

Below is a comparison of the properties of carotene and vitamin A.

Carotene	Vitamin A
Synthesized by plants	Stored by animals
Reddish-yellow in color	Almost colorless
Absorption band at 328 mμ absent	Absorption band at 328 mμ present
Greenish-blue color reaction with antimony trichloride giving absorption band maximal at 590 mμ	Vivid blue color with antimony trichloride, absorption band maximum between 615 and 620 mμ

The manner in which vitamin A exerts its action is not known precisely, but it probably acts in chemical combination with other substances as an oxidation-reduction catalyst.

A second vitamin A, called vitamin A₂, is present in some fish-liver oils, but, except in those from fresh-water fish its concentration is very much lower than the vitamin derived from β -carotene. This latter form is now often referred to as vitamin A₁. Vitamin A₂ is believed to differ chemically from A₁ in possessing an additional CH₃ group and an extra conjugate double bond. In antimony trichloride it shows an absorption band maximal at 696 m μ . It is the predominant form found in the livers of fresh-water fish (see p. 970) but has not been obtained from the livers of mammals.

The relation of vitamin A₁ to rhodopsin and of A₂ to porphyropsin is outlined in Chapter XXV.

The importance of vitamin A in nutrition and bodily welfare

The following effects result from vitamin A deficiency, which may be due not only to a dietary lack but also to failure in absorption, as in obstructive jaundice and sprue, or to severe liver disease (e.g., cirrhosis) in which the carotene conversion process is impaired.

(a) *Failure to gain in weight.* Since young rats upon diets lacking in vitamin A fail to increase in weight it was thought at first that this vitamin had a specific growth-promoting effect. It has been shown, however, by Orr and Richards from measurements of body length and lengths of limb bones that growth in the true sense is not arrested by vitamin A deficiency. Skeletal growth continues though the animals fail to gain in weight. The weight curve is therefore not a true index of skeletal growth.

(b) *Disorders of the skin.* In man, one of the earliest manifestations of vitamin A deficiency is dryness of the skin followed by a papular eruption due to changes in the hair follicles; the sebaceous glands and sweat glands atrophy. Hyperkeratosis and the formation of keratotic plugs in the hair follicles are seen in man and in rats.

(c) *Xerophthalmia and inflammatory eye conditions.* In xerophthalmia the primary change appears to be in the lachrymal glands whose secretion is suppressed. The corneal surface becomes dry and, having lost the protective and lubricating effect of the tears, becomes invaded by micro-organisms (fig. 249). Inflammation and thickening of the conjunctivae with a purulent discharge, and softening (keratomalacia) leading to ulceration

of the cornea result. Osborne and Mendel observed this condition in 80 per cent of rats placed upon a vitamin A deficient diet. It occurs in the human subject when the diet is lacking in this vitamin and there is no doubt that it is a specific manifestation of such deficiency, since it cannot be produced in animals by the lack of any other vitamin.

(d) *Cornification of epithelial surfaces.* The epithelial linings of the respiratory, alimentary and urinary tracts and the ducts of various glands, tend to become converted to the stratified squamous type with consequent drying up of their secretions. Evans and Bishop observed that the cornified



FIG. 249. Illustrates a baby which had suffered from an attack of ophthalmia of dietary origin, and was cured by administration of fat-soluble A as butter and cod-liver oil. The disease had, however, progressed so far that the sight of the left eye was destroyed and the right eye damaged. (After Bloch, from McCollum and Simmonds, *The Newer Knowledge of Nutrition*.)

vaginal cells characteristic of the estrous period of the rat (p. 747) appeared in animals upon a diet deficient in vitamin A even though the ovaries had previously been removed. The changes in the lachrymal glands, hair follicles and cutaneous glands mentioned above, as well as several other manifestations are special examples of the general tendency toward cornification of epithelial tissues when the diet is deficient in vitamin A.

(e) *Night blindness (hemeralopia or nyctalopia).* This is the failure of vision in dim light which occurs in man and animals as a result of vitamin A deficiency. It is not uncommon in the tropics, and an interesting example of custom anticipating science is the fact that the native treatment for the condition was a poultice of liver to the eyes and the addition of liver to the diet. Night blindness

is also seen in Labrador and certain parts of Newfoundland where the diet in winter is deficient. The condition is due to the failure in regeneration of the visual purple (p. 970) after the eyes have been exposed to bright light. In health, regeneration of the pigment occurs after the eyes have been a few minutes in the dark; whereas in vitamin A deficient animals (rats) the regeneration occurs very slowly or not at all. The relation of vitamin A to the formation of visual purple has been investigated by Wald (p. 970).

It should be emphasized that vitamin A deficiency is not the only cause of night blindness, and even when it is the cause the visual defect cannot always be attributed to failure in the regeneration of visual purple, for degenerative changes in the visual receptors or of the neural elements of the retina may be a relatively early effect.

A method has been devised for detecting mild grades of vitamin A deficiency based upon the measurement of the rate of dark adaptation. The eyes are first accustomed to complete darkness for a period of 10 minutes and then exposed to a bright light seen through the eyepiece of a specially designed photometer (or adaptometer) for 3 minutes. The light is then switched off and the rate of dark adaptation determined for a period of 10 minutes. The clinical value of this test is in some doubt. The determination of the concentration of the vitamin in the plasma is a more sensitive and reliable test. Some believe that impairment of the faculty of dark adaptation, due to mild grades of vitamin A deficiency, may be a contributory factor in many motor accidents occurring at night.

(f) *Degenerative changes in the nervous system.* Mellanby reported that there occurred in dogs upon a diet rich in cereals and deficient in vitamin A a condition resembling subacute combined degeneration of the cord in man (p. 868). Wolbach and Bessey conclude, however, from their experiments upon growing rats that the effect of vitamin A deficiency upon the nervous system is not direct, but is of mechanical origin due to the retardation of the growth of the bones of the vertebral column.

There is some evidence that vitamin A deficiency in man in certain instances leads to optic neuritis. Degenerative changes in the layers of the retina including the outer portions of the rods have been described as resulting from vitamin A deficiency and it is probable that the changes in the rods are responsible, in many instances, for night blindness in vitamin A deficiency. Degeneration of other cranial nerves, especially of sensory fibers, were also observed in Mellanby's animals and is

due most probably to pressure by bony overgrowth.

(g) *Susceptibility to infections.* In animals, abscesses at the base of the tongue; genito-urinary and respiratory infections; abscesses of the middle ear and nasal sinuses, as well as the inflammatory eye conditions already mentioned, are very frequent results of vitamin A deficiency. Also, mice upon A-deficient diets succumb more readily than do normal mice to the administration of paratyphoid cultures (Lassin).

In considering the possibility that the foregoing results of vitamin A deficiency in animals have a bearing upon similar infective conditions in man the question must be considered from two points of view: (a) Is the vitamin A content of the diet in a proportion of the general population actually reduced to a level at which such infective conditions are likely to arise? (b) Does vitamin A in excess of the quantity present in a diet, judged by

Cervical Segment I

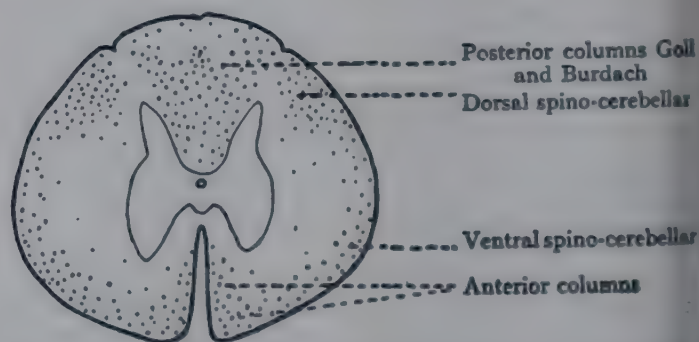


FIG. 250. Shows degeneration in spinal cord of dog fed on a vitamin A-deficient diet. (After E. Mellanby *Nutrition and Disease*.)

the usual criteria to be quite adequate, raise the resistance of the individual, and so serve a preventive or curative function in infective processes? With regard to the first question:—the diets of the population of this continent, according to Hess and his colleagues, is rarely deficient in vitamin A, that is, lacking to the degree at which the generally recognized signs of vitamin A deficiency appear. Nevertheless, it is still possible that a vitamin A intake somewhat above this level is required to maintain a high resistance against ordinary infective processes, and that in this sense a mild degree of vitamin A deficiency is not uncommon. This is a difficult question to decide, but there is little evidence that such is the case. The vitamin A stores of persons dying of infective diseases are not lower than the stores of those dying from other causes. When the vitamin A deficiency, however, reaches the point where skin disorders or xerophthalmia develop it is to be expected that, as in

animals, the susceptibility to various infective conditions will be increased. One can readily believe that the changes in the epithelial surfaces (cornification) mentioned above would be conducive to infective processes, since healthy mucous membranes constitute a "first line of defence" against the invasion of microorganisms.

With regard to the second question:—does vitamin A in excess, i.e., above the quantity contained in the average diet, exert a specific prophylactic or curative action in respect to infective processes generally? The evidence is conflicting. Mellanby and Greene believe as a result of their investigations that vitamin A concentrates increase the resistance to puerperal sepsis and septicemia. They have spoken of vitamin A as the anti-infective vitamin. They reported that in cases treated with the vitamin before confinement the incidence of septic conditions was very much lower than in those not treated. They also stated that the mortality rate of a group of septicemic cases treated with the vitamin (and receiving a diet of high nutritional value as well) was less than a third of that of cases treated in the usual way. Ellison found that in a series of pneumonia cases secondary to measles the mortality in those receiving vitamin A was less than half that in the same number of control cases, and Donaldson and Tasker reported that the mortality rate of adult pneumonia patients treated with vitamin A was 44 per cent lower than that of patients to whom the vitamin had not been administered. Other observers, however, have been unable to demonstrate any beneficial effects of the vitamin upon the incidence or course of various infections, respiratory, pharyngeal, aural, etc., or of the common cold provided that no actual vitamin A deficiency existed. Hess could observe no beneficial effect—gain in weight or increased immunity—in infants as a result of adding vitamin A to the diet. Also in an investigation carried out by Mackay upon infants the incidence of general infections was not reduced in the group receiving vitamin A. Nor did Ellison find that the administration of the vitamin reduced the incidence of ear disease following measles. Since no unequivocal evidence of vitamin A having a specific anti-infective function has been brought forward, the question must remain undecided for the present. It seems wiser, quoting Mendel, "To stress the indefinite function of the vitamin in preserving 'health and vigor' rather than to herald any specific action against definite microbiotic enemies." This probably applies equally well to other vitamins.

(h) An antagonism between vitamin A and the thyroid hormone has been demonstrated. The loss in weight of rats caused by daily injections of thyroxine can be prevented by the administration of carotene. It has also been shown that the stores of vitamin A in the livers of guinea-pigs are reduced by injections of thyroxine and the metamorphosis of tadpoles treated with thyroxine can be delayed by treatment with vitamin A. It appears that the thyroxine effect is due to its causing rapid destruction of the vitamin and not because it prevents the conversion of the provitamin. Indeed in *hypothyroidism* the conversion of carotene to the vitamin is defective; the milk of goats, which ordinarily is pure white, becomes yellow after thyroidectomy, due to the excretion of unchanged carotene.

(i) *Renal function.* Pathological changes in the kidneys have been reported by several workers as resulting from vitamin A deficiency in animals as well as in man. Vacuolization and calcification of the cells of the convoluted tubules, cloudy swelling of the cells of the collecting tubules and hyperplasia and cornification of the epithelium of the renal pelvis have been described. The experiments of Herrin and Nicholls indicate that vitamin A plays an important rôle in renal physiology. They demonstrated a reduction up to 40 per cent in the urea clearances of dogs upon vitamin A deficient diets. The clearances were restored to normal by the administration of adequate amounts of the vitamin. On the other hand, the urea clearances were raised by from 42 to 100 per cent above the normal in dogs receiving large doses of vitamin A.

(j) The relationship of vitamin A to urinary lithiasis is discussed on p. 721.

THE VITAMIN B COMPLEX

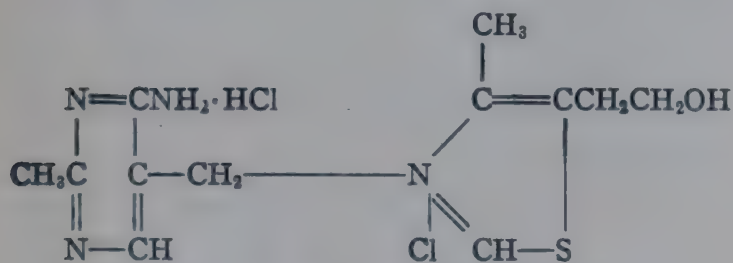
The first vitamin to be discovered was called the antineuritic vitamin since its absence from the diet was shown to be the cause of beri-beri (see below). When the practice was adopted of referring to the vitamins by letter it was designated vitamin B. Later work showed it to be a combination of several vitamins, one is antineuritic and now known as vitamin B₁ or *thiamin*; the other components of the B complex are, *riboflavin*, *nicotinic acid* or *niacin*, *pyridoxin*, *pantothenic acid*, *inositol*, *biotin*, *para-aminobenzoic acid* and *choline*.

The grouping together of these water soluble vitamins under the heading, B complex, is not artificial and simply a convenience, but based upon a common wide distribution and close association in vegetable and animal tissues, and upon their intimate functional interrelationships. They are of importance for the growth or metabolism of various forms of life from bacteria, protozoa and yeasts to mammals. They presumably form an essential part of the enzyme systems underlying

living processes. Several have been shown to be synthesized, to some degree at least, by bacteria in the intestinal tract of higher animals.

THIAMIN⁴ OR VITAMIN B₁ (ANTINEURITIC)

Chemical properties of B₁. This factor is soluble in water and in 70 per cent alcohol or acetone. In acid media it is resistant to heat, remaining active for several hours after heating, with free access of air, to 100°C. It is, however, less resistant to heat than B₂, being destroyed at high temperatures (autoclaving), and is therefore spoken of as the *heat-labile* factor of the B complex, the B₂ factor being referred to as the *heat-stable* factor. B₁ is resistant to strong acids but is readily destroyed by alkali. It is adsorbed from solution by Fuller's earth. It was isolated as the chloride in crystalline form by Jansen and Donath in 1926. 0.002 mg. of this preparation was stated to cure polyneuritis in pigeons. It was given the following tentative formula by Windaus and his associates—C₁₂H₁₈N₄OSCl₂. This is the only vitamin containing sulphur and for this reason has been named *thiamin*. Thiamin was synthesized by Williams in 1936. The following is the structural formula of thiamin chloride hydrochloride.



Thiamin chloride hydrochloride

Distribution and requirement. The chief sources of vitamin B₁ are, liver, kidney, lean meat, especially pork, the germ of wheat, rye or corn rice polishings, soy bean, peanuts, and green or dried peas and beans. Smaller amounts are present in egg-yolk, fresh milk, potatoes, turnips, bananas and various nut kernels. The several factors of the B complex tend to show roughly parallel distributions; foods, for example which have a high content of thiamin are generally rich in other B factors.

The daily adult human requirement is around 0.6 mg. per 1000 calories.

Effects caused by vitamin B₁ deficiency

(a) *Beri-beri—polyneuritis.* Beri-beri is a disease which for centuries has been prevalent in rice-

⁴ Also spelled *thiamine*.

eating countries, e.g., Japan, China, India, Dutch Indies, Philippine Islands, etc. It is also occasionally seen in Labrador and Newfoundland and in young children upon deficient diets. The disease is characterized by inflammation of the peripheral nerves (polyneuritis) which leads to progressive paralysis of the limbs and sensory disturbances. There is also dilatation of the right heart. The disease occurs in two forms one with edema (wet type) the other without (dry type). The first definite indication that beri-beri was of dietary origin was obtained (1885) by Takaki, a medical officer of the Japanese Navy who by revising the



FIG. 251. Upper photograph, dog, showing polyneuritis with marked paralysis of hind limbs as a result of a diet lacking in vitamin B. Lower photograph, the same animal cured by vitamin B, given in the form of tomato juice. (After Cowgill and Mendel.)

diet of the sailors practically eradicated the disease from the service. He thought however that the disease was due to protein deficiency and replaced a part of the polished rice of the diet by meat, milk, wheat and barley. The experimental investigation of beri-beri dates from 1890 when the Dutch physician Eijkman observed a disease in fowl at his laboratory in the Dutch West Indies which he believed was of the same nature as the human condition. The affected fowl had received a diet of polished rice, i.e., rice from which the pericarp (bran) and germ had been removed by milling (see fig. 259, p. 661). It was soon shown by

others (Fraser and Stanton) that the condition in fowl and beri-beri in man could be cured by the addition of rice polishings to the diet or an extract prepared from them. The subsequent preparation by Funk of a crystalline substance of high antineuritic potency from rice polishings has been mentioned (p. 635).

Polyneuritis is readily induced in pigeons by a diet composed exclusively of polished rice. Retraction of the head and paralysis of the limbs are outstanding features. B₁ deficient diets cause analogous symptoms in dogs and rats (see fig. 251). The oxygen consumption of the brain tissue is reduced. An accumulation of lactic acid in the hind-brain (Kinnersley and Peters), liver, heart and muscles of birds occurs in the advanced stages of the disease and the lactic acid of the blood is raised. The head retraction is probably due to the increased concentration of lactic acid in the brain substance; the symptom is quickly abolished by the local injection of the vitamin. A high carbohydrate diet intensifies the effects of B₁ deficiency which fact taken together with the high lactic acid concentration just mentioned, suggests that a fault in carbohydrate metabolism (possibly with the formation of toxic substances) exists. Hyperglycemia and depletion of liver glycogen occur in polyneuritic pigeons. Though this may be due in part to inanition, for Drummond and Marrian observed it in starved pigeons receiving adequate amounts of vitamin B₁, it is mainly a direct effect of the avitaminosis. The abnormally high glucose tolerance curves (i.e., reduced glucose tolerance) of rats showing signs of B₁ deficiency also furnish evidence of a disturbance of carbohydrate metabolism (Lepkovsky and associates). *In vitro* experiments indicate that an action of B₁ is to aid in the oxidation of carbohydrate in the brain through the lactic acid stage. For example, sliced brain tissue from an animal (pigeon or rat) suffering from vitamin B₁ deficiency does not consume the normal amount of oxygen when lactic acid is added to it; pyruvic acid also appears in the avitaminosis brain tissue but not in the normal brain. The addition of vitamin B₁ partially corrects these defects; the oxygen usage is increased and the production of pyruvic acid is reduced. The vitamin exerts a negligible effect upon the respiration of healthy brain tissue. The removal of pyruvic acid is normally, according to Peters, an oxidative process, dependent upon an enzyme, pyruvate oxidase, which cannot function in the absence of thiamin. Thiamin (either free or as the pyrophosphate) is thus considered to be a

coenzyme⁵ for pyruvate oxidase, acting in the enzyme system of the tissues as a hydrogen transporter. The accumulation of pyruvic acid inhibits in turn the removal of lactic acid. Failure in the disposal of both these intermediaries of carbohydrate metabolism therefore occurs in the avitaminosis brain.

The vitamin B₁ requirement is influenced by several factors, e.g., the nature of the diet, the quantity of food consumed and the basal metabolism. It is increased by a diet high in carbohydrate but reduced by one high in fat. The onset of polyneuritis in pigeons on a low B₁ intake, for example, is hastened if the caloric intake is made up largely of carbohydrate and delayed by replacing a part of the carbohydrate by fat. Evans and Lepkovsky showed that the thiamin requirement for the growth of rats was considerably lowered by a high fat diet. This effect of dietary fat is spoken of as its "sparing effect" upon the B₁ requirement. It does not appear, however, to be a true sparing action, for no significant difference is demonstrable between the thiamin content of the tissues of B₁ deficient animals on high and low fat diets, respectively. The experiments of McHenry and his associates indicate a relationship between the actions of choline, thiamin and fat metabolism. They found that in young rats on a choline-free diet an increase in the body fat and liver fat follows the oral administration of B₁. If vitamin B₁ is lacking from the diet, a low choline intake is followed by an increase of liver fat for a short time only—presumably, only until the body stores of B₁ are exhausted. These observers, as well as Whipple and Church, suggest that vitamin B₁ influences the conversion of carbohydrate (possibly via pyruvate) to fat.

(b) *Arrested growth* (fig. 252). Osborne and Mendel found that "protein-free" milk supplied a substance necessary for the growth and well-being of rats. They concluded that this substance was identical with the antineuritic vitamin. It is now recognized that B₁ as well as other factors of the B complex influence growth. Loss of appetite, which leads to undernutrition, is, however, a contributory factor in the retardation of growth resulting from a deficiency of this vitamin. In infants the failure to gain at the normal rate though the diet appears to be adequate, is considered in some instances to be due to a low B₁.

⁵ Thiamin does not serve merely as an activator of the enzyme, as the term coenzyme might lead one to suppose, but is regarded as an integral part of the enzyme molecule.

intake. Tisdall has reported that in a group of young children to whom a concentrate of the B complex was administered, the rate of weight gain over a period of seven months was 1.6 times that of a control group on the same diet but receiving no additional supply of the vitamin.

(c) *Loss of appetite and atony of the gastro-intestinal tract.* Loss of appetite is an early effect of vitamin B₁ deficiency, being evident some time before the appearance of polyneuritis. It occurs in rats and dogs and in human beri-beri. It is probable that the anorexia is, in part at least, secondary to a relaxed state of the gastro-intestinal

plex, notably, pantothenic acid, have a greater influence.

(d) *Bradycardia (in rats and pigeons).* Marked cardiac slowing was observed by Carter and Drury in pigeons fed upon polished rice; it was shown to be due to increased tone of the vagus center; it is abolished by vagal section or atropinization. Drury, Harris and Maudsley observed an extreme degree of bradycardia in rats upon diets deficient in vitamin B₁ but in these animals it is not of vagal origin; it arises in the sinus node. The administration of material rich in vitamin B₁ restores the cardiac rate to normal within an hour or so. It has been shown by Birch and Harris that lactic acid accumulation in the cardiac tissue is associated with the phenomenon.

(e) *Alcoholic psychoses* are believed in many instances to be due, in part at least, to a deficiency of the antineuritic vitamin. The addict receives a large proportion of his caloric requirement in the form of alcohol which is vitamin free. Vitamin B₁ deficiency, rather than a direct toxic effect of alcohol, is held responsible for the aggravation of preexisting cardiac disease and the precipitation of cardiac failure (if not for originating it) which is of such frequent occurrence in chronic alcoholism. In other words, the drunkard may show in varying degrees the cardiac features of beri-beri. The low storage capacity of the body for thiamin as compared with that of the other vitamins apparently accounts for the fact that signs of deficiency of the former are the first to make their appearance.

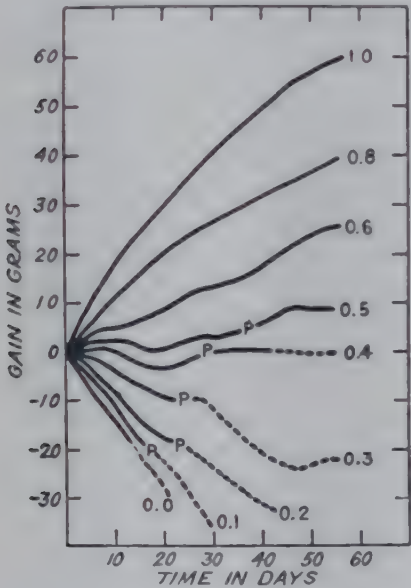
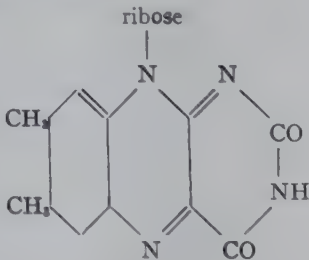


FIG. 252. Average gain curves of rats on vitamin B-free diet plus daily supplement of ground whole wheat of 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.8 and 0.10 grams. Negative controls (marked 0.0) received basal diet only. *P, point where, on the average, chronic symptoms of polyneuritis appeared. Lines broken from the points at which some individuals died. (After Chase, from Sherman and Smith, *The Vitamins*.)

musculature and the reduction in motor activity of the gastro-intestinal tract which have been shown by Cowgill and associates to be important features of vitamin B₁ deficiency. McCarrison produced atony of the bowel and degeneration of the mucous membrane of the colon in monkeys by feeding diets lacking in the B₁ vitamin but of high carbohydrate content. It is not unlikely that in many diets which are assumed to be adequate, the B₁ content is below the optimal level, and that gastro-intestinal abnormalities are not uncommonly the result of mild grades of deficiency of this vitamin, or other factors of the B complex. Recent work indicates that the effect of thiamin upon gastro-intestinal function has been exaggerated and that other components of the B com-

*Riboflavin*⁶ belongs to a group of yellow fluorescent pigments called *flavins*. This factor is responsible for a part of the growth promoting property of the B complex. The flavins are soluble in aqueous media and for this reason are called aqueous media and for this reason are called lyochromes as distinguished from the fat soluble pigments—the lipochromes. Flavins are widely distributed in animal tissues—liver, kidney, milk, etc. Riboflavin, has been synthesized, and has the following formula:



Riboflavin

⁶ Confusion in terminology sometimes arises owing to the fact that riboflavin is referred to by some as vitamin B₂ or as vitamin G.

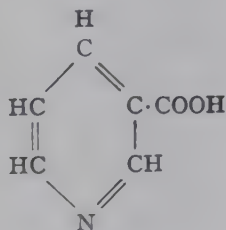
The daily adult human requirement of riboflavin is between 2 and 3 milligrams.

Riboflavin undergoes phosphorylation forming the mononucleotide riboflavin phosphate which is bound as a prosthetic group to protein. The resulting *flavoprotein* can act as an acceptor and as a donator of hydrogen ions (see p. 330).

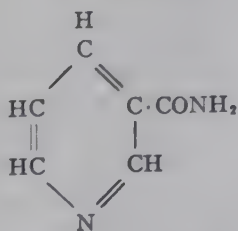
In man riboflavin deficiency has been recognized as the cause of certain well defined ocular lesions. In the milder grades of deficiency, examination with the slit lamp (p. 992) reveals congestion of the vessels of the limbic plexus at the periphery of the cornea and the invasion of the subepithelial layer of the cornea by loops of capillary vessels. When the deficiency is more severe the vascularization of the cornea is obvious to ordinary inspection; the eyes appear bloodshot. Burning, itching and lachrymation are complained of. There is photophobia which may be so severe as to prevent the eyes from being opened. Interstitial keratitis may be a later development. Another effect of riboflavin deficiency is the development of fissures and sores at the mucocutaneous margin at the angles of the mouth (*cheilosis*).

Nicotinic acid (niacin) and nicotinic acid amide (pellagra preventive factor)

Chemistry, metabolism and function. The formula of nicotinic acid and nicotinic acid amide are shown below:—



Nicotinic acid



Nicotinic acid amide

Nicotinic acid, though related to nicotine (from which it can be derived through oxidation by nitric acid or potassium permanganate), does not exhibit the action of nicotine upon the autonomic nervous system and is relatively non-toxic. It

does, however, cause peripheral vasodilatation with flushing of the skin when injected intravenously. Nicotine absorbed in smoking cannot be converted into the vitamin. Trigonelline and nicotronic acid are end products of nicotinic acid metabolism; after the administration of the vitamin to man, the dog or the rat, these substances appear in the urine.

Synthesis of nicotinic acid has been shown to occur in rats, sheep and chicks and is brought about largely by bacterial action in the intestine, though in the chick, at any rate, synthesis also appears to be a function of the body tissues.

This vitamin acts principally as a hydrogen transporter in tissue respiration. Co-enzyme I (diphosphopyridine nucleotide) (p. 330) and co-enzyme II (triphosphopyridine nucleotide) are derivatives of nicotinic acid amide. A reduction of the former enzyme has been demonstrated in the tissues of animals suffering from nicotinic acid deficiency. The concentration of these enzymes in the blood of normal human subjects, as well as of those suffering from pellagra is raised by the administration of nicotinic acid. The function of this vitamin is closely associated with the metabolism of carbohydrates, the requirement being raised in diabetes when the consumption of carbohydrate or the insulin dosage is increased.

Sources and requirement. Liver (especially pork liver) kidney, brewer's yeast, whole rye, wheat germ, soy bean and peanuts, are among the richest sources of nicotinic acid. Other good sources are, bananas, almonds, beans, and wheat bran. The daily adult human requirement lies between 20 and 30 mg.

Effects of nicotinic acid deficiency

Deficiency of nicotinic acid or its amide is the cause of the main symptoms of *pellagra* and of the condition in dogs known as "*black tongue*."

Pellagra. The chief features of pellagra (= rough skin) are patches of dermatitis, redness and soreness of the tongue together with digestive disturbances and diarrhea. Nervous disorders (muscular weakness, tremor paresthesias) may occur, and in the later stages melancholia, dementia or delirium. The skin lesions consist of redness, dryness and the formation of scales upon surfaces exposed to the sun's rays, e.g., the backs of the hands (or the insteps of persons who go barefoot), the neck, cheeks and bridge of the nose. A reddish pigment is excreted in the urine. Degeneration of the spinal tracts, especially of the posterior columns, and of nerve cells in brain and cord is not uncommonly seen post mortem.

Just as beri-beri is a disease affecting those who subsist mainly upon a diet of polished rice, so pellagra is a maize-eater's disease. The condition results whether the maize is whole or has had the pericarp and germ removed. It is prevalent among the poor of the Southern United States, of Spain, Italy and other European countries. It is rare in England, Canada and the Northern United States. The dietary origin of pellagra was clearly demonstrated by Goldberger. He carried out an experiment upon twelve prisoners who in return for a promise of pardon volunteered to submit to a diet of cornmeal, cornstarch, rice, syrup, sweet potatoes and pork fat. At the end of six months pellagra was diagnosed in half the subjects. The other prisoners who received the ordinary institutional fare showed no signs of the disease. At first, Goldberger thought that the disease was due to protein (amino-acid) deficiency but as a result of subsequent experiments upon animals came to the conclusion that a vitamin deficiency was the principle causative factor, and it soon became evident that autoclaved yeast, wheat germ and other substances rich in vitamin B would prevent or cure pellagra.

Most subjects of pellagra also suffer from deficiencies of other factors of the B complex, the administration of nicotinic acid alone being as a rule insufficient to effect a complete cure.

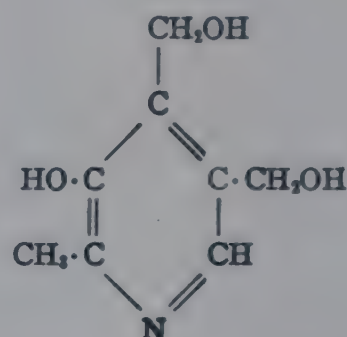
"Black tongue" in dogs is a condition analogous to human pellagra. Necrotic areas appear upon the tongue and the buccal mucosa, and a pellagra-like dermatitis of the scrotum develops in animals receiving a diet free from vitamin B₆. A pellagra-like condition also develops in rats upon diets lacking in this vitamin.

Until the last few years the factor in the B complex which prevents pellagra (P.P. factor) had eluded discovery. Funk as early as 1911 reported the presence of *nicotinic acid* in his extracts but its physiological significance was not realized. Warburg recognized its presence in association with tissue respiratory enzymes and was aware of its fundamental importance in the oxidative processes of the cell. In 1937 Elvehjem and his colleagues isolated nicotinic acid and its amide from liver and discovered that it cured "black tongue" in dogs. Shortly afterwards it was used with outstanding success by Spies and his associates in the treatment of pellagra.

Certain mental and neurological manifestations, e.g., clouding of consciousness, rigidities and unusual grasping and sucking reflexes have been

attributed to nicotinic acid deficiency. Improvement has followed administration of the vitamin.

Pyridoxin or Vitamin B₆ (antidermatitis factor) Rats upon a diet lacking in vitamin B₆ develop skin disorder (rat dermatitis or acrodynia) characterized by redness, scaliness and loss of hair. It is now agreed that the antidermatitis effect is due to the B complex which has been recognized for years. Vitamin B₆ was synthesized by Harris and Folkers in 1939. It has the following formula:



Pyridoxin (2-methyl-3-hydroxy-4,5-dihydroxy-methyl) pyridine

Spies and Ashe have reported that certain symptoms in pellagrins and subjects of beri-beri, namely extreme nervousness, insomnia, irritability, abdominal pain and difficulty in walking, which are not relieved by nicotinic acid, thiamin, or riboflavin, are abolished in dramatic fashion by pure B₆ (synthetic).

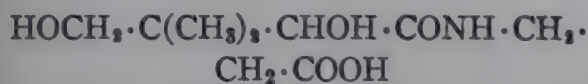
There are also indications that this vitamin is of importance in hemoglobin synthesis and in the manufacture of red cells. Dogs and pigs on a diet deficient in pyridoxin develop a hypochromic microcytic anemia which is quickly cured when the deficiency is corrected. Also, in rabbits rendered anemic by repeated bleedings, hemoglobin regeneration and erythrocyte production are hastened by the administration of pyridoxin. The vitamin is also necessary for the normal growth of rats; an assay method is based upon this fact.

The essential importance of B₆ in the life of many lower forms has been demonstrated. It is necessary for the growth of yeast, of mosquito larvae and of several types of microorganisms (Streptococcus hemolyticus, Staphylococcus albus and lactic acid bacillus).

The richest sources of pyridoxin are certain vegetable fats, wheat germ, yeast, legumes, and meat products, especially muscle and kidney. Benefit from its use has been reported in Parkinsonism, muscular dystrophy and myasthenia.

gravis, but hopes that it would be of real value in these nervous disorders have been on the whole disappointed.

Pantothenic acid (chick antidermatitis factor). This component of the B complex has the following formula:—



Pantothenic acid (α - γ -dehydroxy- β , β -dimethylbutyryl-aminopropionic acid)

It was found by Williams and his associates in extracts of various plant and animal tissues and was shown to stimulate the growth of yeast. Like the other factors of the B complex already considered, pantothenic acid has been synthesized. Its identity with the factor which for some time has been recognized as preventing dermatitis in chicks is now established. Lesions of the spinal cord and eye symptoms are also produced in chicks by a deficiency of this factor. It is necessary in the diet of the hen for the hatchability of the eggs, and for egg-laying in pullets. This vitamin has a very wide distribution but the richest dietary sources of this vitamin are liver, kidney, egg-yolk, wheat bran, brewer's yeast, broccoli, molasses and peanuts.

The rôle played by pantothenic acid in human nutrition has not been elucidated, though its function appears to be bound up with that of riboflavin. Its concentration in the blood of subjects of pellagra, beri-beri and of riboflavin deficiency is from 23 to 50 per cent (Spies) below normal, and a rise in the riboflavin content is accompanied by a corresponding rise in pantothenic acid.

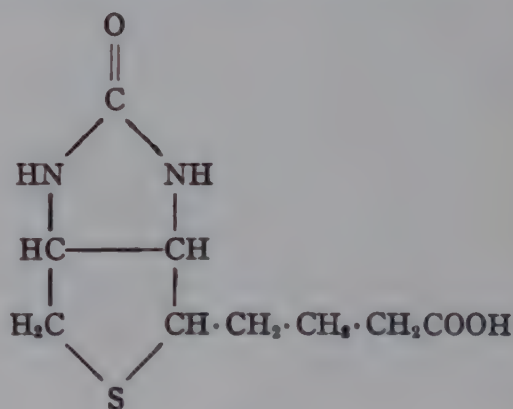
Renal, adrenal and cardiac damage and dehydration of the tissues are found in rats with pantothenic acid deficiency. There is also an increased appetite for salt, which is probably the result of the adrenal defect. This vitamin has been termed an anti-gray hair factor since it prevents graying of the fur in black rats. Depigmentation of the feathers of fowl suffering from a deficiency of pantothenic acid has also been reported. These results upon animals cannot be transferred to man. No definite evidence of a factor which prevents the graying of human hair has yet been secured.

About 3 milligrams of this vitamin are excreted daily in the urine of man.

Inositol. (mouse anti-alopecia factor). $\text{C}_6\text{H}_8(\text{OH})_6$, a carbohydrate is found combined with phosphate in cereals and in the phospholipid

of soy bean. It is also present in liver and muscle. This factor is necessary for the normal nutrition of the mouse. When lacking from the diet of young mice, growth is arrested and hair fails to grow over the trunk. Its function in other species and in human nutrition is unknown, but the possibility of its being of benefit in certain skin lesions, e.g., psoriasis, has been suggested. Inositol is synthesized by bacteria in the intestinal tract, but the presence of pantothenic acid is necessary for synthesis.

Biotin. This factor of the B complex is necessary for the growth of yeast and as a growth stimulant or requirement of certain bacteria and fungi. Its chemical constitution was determined by du Vigneaud and his associates and its synthesis effected by Harris and his colleagues. The structural formula of biotin (2'-keto-3,4,imidazolido-tetrahydrothiophenovaleric acid is shown below:—



Biotin

Rats fed upon egg-white develop a severe dermatitis (egg-white injury) which has been shown to be due to the presence of a protein known as *avidin*. Avidin combines with biotin and by rendering the latter unavailable induces biotin deficiency. Thus, biotin occurs in a bound form (*avidin-biotin*) which is inactive and as a free active form. Biotin is not liberated from its combination with avidin by the digestive, proteolytic enzymes, but separation can be brought about by oxidative procedures, e.g., treatment with hydrogen peroxide. Avidin appears to be associated in some way with the female reproductive functions; stilbestrol administration followed by progesterone causes the production of this protein in the oviducts of immature chicks.

Biotin is found in relatively large amounts in liver and kidney. It is present in lower concentrations in egg-yolk, tomatoes and carrots. Certain types of carcinoma contain it in relatively large amounts. This finding has suggested

the possibility that, by reducing the free biotin content of the diet, inhibition of cancerous growth might be brought about.

Para-aminobenzoic acid. This factor has the following formula:—



Para-aminobenzoic acid

It is essential for the growth of certain micro-organisms and antagonizes the bacteriostatic action of the sulfonamides. The resistance to these bacteriostatic agents which is shown by *Staphylococcus aureus* is due to the ability of this organism to synthesize para-aminobenzoic acid. This factor is also an essential constituent of the diet for the normal growth of chicks and in combination with inositol, prevents decoloration of the hair (achromotrichia) of rats. The effect upon the growth of chicks is probably an indirect one, namely, the stimulation of the growth of intestinal bacteria and the synthesis of known growth-promoting factors

Choline .(See p. 601.)

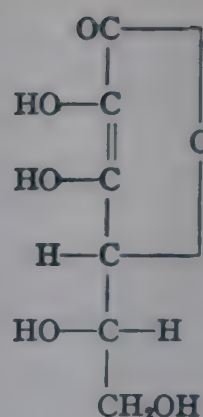
VITAMIN C (ANTISCORBUTIC)

Properties

Vitamin C has been shown to be a relatively simple chemical substance closely allied to hexuronic acid. It has been appropriately named *ascorbic acid* ($C_6H_8O_6$).⁷

Ascorbic acid was isolated by Szent-Györgyi in 1928 from oranges, lemons and cabbages and from the suprarenal cortex. It was shown to have a high antiscorbutic potency. Almost simultaneously King and Waugh obtained crystals of ascorbic acid from concentrates of lemon juice which were capable in 0.05 mg. daily doses of protecting a guinea pig from scurvy. It was later synthesized by Hirst and associates who gave it the following structural formula.

⁷ This is also referred to as *cevitamic acid*, a term recently adopted by the American Council on Pharmacy and Chemistry.



L-Ascorbic acid—Vitamin C

Ascorbic acid has a high reducing power, soluble in water and alcohol, and is readily destroyed by heat, sunlight and oxidizing agent. Prolonged boiling, drying, aging or storage of food reduces or abolishes their antiscorbutic properties. Copper catalyzes the oxidative process, so that the vitamin is destroyed much more readily when foods are cooked in a copper utensil than when glass, enamel or aluminum vessels are employed. Nevertheless, boiling milk even in an enamel vessel for five minutes destroys 20 per cent of its vitamin C content. Heating to 60°C. for thirty minutes (pasteurization) in a copper vessel destroys 80 to 90 per cent of its vitamin C value but only a negligible loss occurs if the pasteurization is carried out in an aluminum or enamel container. In general, slow cooking, e.g., stewing is more destructive to the vitamin than more rapid cooking even at a higher temperature. There is said to be little loss of vitamin C in the commercial canning of fruit.

The essential function of vitamin C appears to be the maintenance in a normal state of the intercellular ground substance in which the tissue cells are embedded and cemented together. The matrix of bone and of dentine, the cement substance between the cells of the capillary walls and the ground substance of the general connective tissues, etc. are produced by the supporting or collagenous cells (e.g., fibroblasts, osteoblasts, etc.). As originally formed the material, according to Wolbach is liquid but after its production becomes, under normal circumstances, transformed into a semi fluid gelatinous mass in which the tissue cells are embedded. It is the view of Wolbach that the gelation process and the maintenance of the gelatinous state are dependent upon the action of vitamin C. The manner in which the antiscorbutic vitamin exerts its effect is unknown. There is ample evidence that it serves as a hydrogen trans

porter in the respiratory enzyme system of plant cells, but evidence of its playing a corresponding rôle in animal tissues is inconclusive. The respiratory activity of scorbutic tissues is not reduced nor does an increase in oxygen consumption result from the addition to such tissues of ascorbic acid.

The distribution of vitamin C

The richest sources of this vitamin are the citrus fruits (oranges, lemons, grapefruit and limes), cabbage, swedes and turnips, tomatoes, spinach, green and red peppers. Fresh meat, cow's milk and other animal foods are very poor sources of vitamin C. Its concentration is several times greater in human milk than in cow's milk. The vitamin is stored to a very limited extent in the body. It is in highest concentration in the adrenal cortex. Of other tissues, the crystalline lens, the corpus luteum and the pituitary gland contain the largest amounts. The average concentration in human blood is from 0.7 to 1.0 mg. per 100 cc. From 30 to 50 mg. are excreted daily in the urine.

The synthesis of vitamin C

The precursor from which vitamin C is synthesized in Nature is unknown, but glycuronic and galacturonic acids are likely possibilities. It is synthesized by germinating seeds and in the growing sprouts and tips of plants which contain it in relatively high concentration, whereas it is absent, or nearly so, from dried seeds and the less actively growing plant tissues. Ascorbic acid is formed by the chick embryo and apparently by the adult fowl, the rat, mouse and dog, but not by the guinea pig, the monkey or man. The particular tissue responsible for the process is unknown; it is not dependent, entirely at any rate, upon the adrenals since adrenalectomized rats and dogs survive upon a diet free from vitamin C. This vitamin is now synthesized on a commercial scale from glucose, sorbitol being an intermediate product.

The effects of vitamin C deficiency

Scurvy (scorbutus). The essential pathological change in scurvy is weakening of the endothelial wall of the capillaries;⁸ the intercellular cement substance is reduced in amount. This leads to hemorrhages from various structures, e.g., mucous

membranes of the mouth and gastro-intestinal tract, skin, subcutaneous tissues, muscles and subperiosteal tissues. Redness, swelling, ulceration and, in severe cases, gangrene of the gums result. Some of the main features of the condition are: anemia; small cutaneous hemorrhages (petechiae); pains in the bones and tender swellings, due to subperiosteal or muscular hemorrhages; separation of the epiphyses, especially in young children; great weakness and emaciation. X-ray examination of the scorbutic bone shows a white line running down the outside of the shaft which is not seen in normal bone. In guinea pigs, the clotting time of the blood is prolonged and the platelets and red cells are reduced. There is a progressive reduction in the ascorbic acid content of the adrenal cortex in guinea pigs upon a scorbutic diet; the addition of orange juice to the diet restores the normal content.

In the past, scurvy as an adult disease occurred most frequently upon sea voyages, since fresh food for perhaps months at a time was lacking from the diet. For a similar reason it occurred during military campaigns and exploration parties, or in the general population in times of famine. During world war I it made its appearance among members of expeditions in the East, and among civilians in some of the warring nations. It may also develop in artificially fed infants (*Barlow's disease*). According to Drummond the vitamin C content of the diet of adults is frequently, even at ordinary times, only a little above the level at which scurvy appears. Such grades of vitamin C deficiency may, however, be the cause of anemia, adequate supplies of the vitamin being required apparently for the normal functioning of erythropoietic tissue. Among other pathological conditions in which, in some instances, vitamin C deficiency may play a rôle are, cataract, gastric ulcer and rheumatic fever. However, the evidence adduced to connect hypovitaminosis C with these conditions is inconclusive.

One of the earliest records of the cure of scurvy by the administration of a substance rich in vitamin C is that describing an episode of Jacques Cartier's second voyage to Canada (1535). A number of the explorer's men had died from scurvy and most of those remaining were dangerously ill. These were cured by a drink prepared by a friendly Indian from the leaves and bark of an evergreen tree (probably the spruce).

About the middle of the eighteenth century (1747) Lind, a British naval surgeon, carried out

⁸ The capillary resistance test is described on page 95.

an interesting and entirely admirable clinical research, the results of which showed conclusively the antiscorbutic value of oranges and lemons.

Lind, as he says, "took 12 men in the scurvy on board the 'Salisbury' at sea. Their cases were as similar as I could have them. They all had putrid gums, the spots and the lassitude with weakness of their knees." He grouped them into six pairs. To one pair he gave daily a quart of cider, to another pair elixir vitriol, to the third pair vinegar and to the fourth sea water and an electuary composed of garlic, mustard seed, balsam of Peru and myrrh, together with acidulated barley water as a drink. The fifth pair each had a lemon and two oranges daily. "The consequence was," he records "that the most sudden and visible good were perceived from the use of the oranges and lemons; one of those which had taken them being at the end of six days fit for duty . . . the other was the best recovered of any in his condition . . . and was appointed nurse to the rest of the sick." He also noted some good effect from the cider but none from the other articles. Lind recommended that concentrated lemon juice be rationed to the navy. This advice was not put into effect by the government until 1795, after which the sobriquet "Lime juicer" was given by other nations to the British sailor.

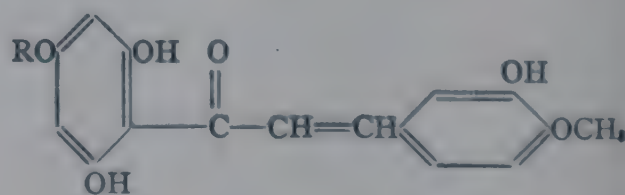
The experimental investigation of scurvy may be taken to date from the work of the Danish scientists Holst and Frohlich (1907 to 1912) who found that the condition developed in guinea pigs kept upon a diet completely lacking in green vegetables, e.g., one constituted solely of cereals. It is possible to induce scurvy only in those species which are incapable of synthesizing the vitamin, namely, in the primates and the guinea-pig.

The vitamin C requirement. Harris and his colleagues have devised a method for determining the vitamin C requirement based upon the urinary excretion of ascorbic acid after a known amount has been given by mouth. Vitamin C is a threshold substance, i.e., it is not excreted in the urine if below a certain level in the blood, which depends in turn upon the requirement or degree of "saturation" of the tissues. If the subject's tissues are "saturated" with vitamin C a large part of the administered dose can be recovered from the urine; if the tissues are "unsaturated" more is retained, the proportion varying with the degree of unsaturation. The vitamin C content of the urine is deter-

mined by titration with 2:6, dichlorophenolindophenol (p. 662). The daily requirement of vitamin C for the adult is from 75 to 100 mg., but it varies considerably. Infections, rheumatic fever and certain other conditions tend to deplete the vitamin stores and therefore increase the amount which must be provided in the diet. Infants require much more relatively to their body weight than do adults. The vitamin stores with which the baby comes into the world are depleted within the first few days and even if breast fed it must receive extra supplies in the form of orange or tomato juice.

Vitamin P (permeability vitamin). Szent-Györgyi and his associates obtained a crystalline substance from lemon juice and Hungarian red peppers which they claimed controlled vascular permeability. This material, which they called "citrin" or vitamin P, was found later to consist of two vegetable dyes (flavonols), *hesperidin* and *eriodictyol glucoside* (demethylated hesperidin). They stated that certain hemorrhagic diseases associated with increased permeability or fragility of the capillary wall were cured by citrin, by lemon juice or by extracts of red pepper but not by ascorbic acid. They found further that the survival time of guinea-pigs upon a scurvy-producing diet was prolonged by vitamin P and that the hemorrhages were less pronounced in those that had received it than in control animals upon the scorbutic diet alone. It was therefore postulated that scurvy was due to a deficiency of both vitamins C and P. After several conflicting reports concerning this vitamin, its existence appears to have been finally established. Its distribution in food stuffs is closely similar to that of vitamin C. Lemon peel is an especially rich source.

The physiologically active principle of vitamin P is believed to be *hesperidin chalcone*. Its formula is:—



Hesperidin chalcone

R is a sugar group.

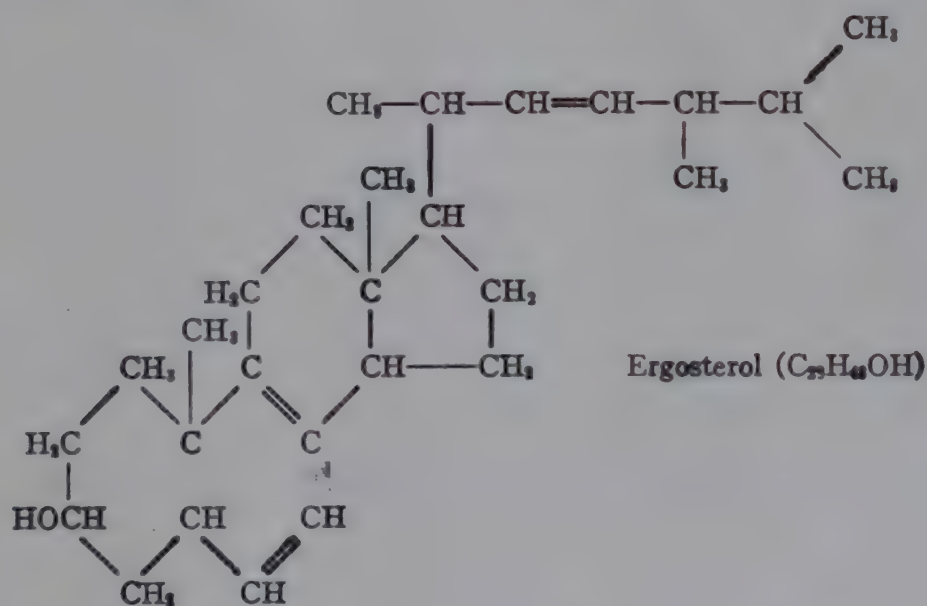
CHAPTER LVI

THE VITAMINS (*Continued*)

VITAMIN D (ANTIRACHITIC)

Properties. Vitamin D is soluble in fats, oils, ether and alcohol but insoluble in water. It is very stable to heat and to oxidation. It shows an absorption band between 260 and 270 $m\mu$ (maximum at 265). The antirachitic vitamin belongs to the class of substances known as sterols or solid alcohols. Among these are *cholesterol* ($C_{27}H_{46}O$) of animal tissues, *phytosterol* of plants, and *ergosterol* found mainly in fungi (yeast, mushrooms, ergot, etc.). *Ergosterol* was first obtained from mushrooms in 1811. The vitamin has been isolated in crystalline form and named *calciferol*.

The following formula has been suggested for ergosterol by Windaus and Langer:



together the antirachitic effects of these and other articles of diet with those of radiant energy. First it was found that when rats on a vitamin D deficient diet were placed in glass jars which had been irradiated by a mercury vapor lamp they thrived as well as if they had been directly irradiated (Hume and Smith). The beneficial effect, as it turned out later, was due to the animals having eaten the irradiated sawdust in the jars. It was also discovered (Goldblatt and Soames) that the livers of rats which had received no vitamin D in their diet but had been irradiated with ultraviolet light acquired antirachitic properties similar to those of cod-liver oil. The livers of non-

ULTRAVIOLET IRRADIATION AND VITAMIN D

The search for the antirachitic vitamin makes one of the most interesting stories of modern biological science. As early as 1890 Palm suggested that sunlight possessed an antirachitic action, and in 1919 Huldchinsky successfully employed the ultraviolet rays from a mercury vapor lamp for the cure of rickets. Hess and Unger demonstrated in 1921 that sunlight had the same curative effect. By this time Mellanby had published his results proving the antirachitic value of cod-liver oil, egg yolk and butter (see p. 655).¹ It was not long before intensive research by several workers furnished the information necessary to link

irradiated rats were quite ineffective. Shortly after this Steenbock and Black and Hess and Weinstock, independently, showed that certain fat-containing foods which possessed no power to cure rickets acquired this power upon artificial irradiation. It was then discovered by these two groups of observers and at the same time by Rosenheim and Webster that cholesterol of animal tissues (skin, brain, etc.) and sterols of vegetable foods gained antirachitic properties upon irradiation. Cholesterol even after careful purification (re-crystallization some 20 times), and though quite inactive if untreated, became powerfully antirachitic upon irradiation. These sterols apparently were the precursors of vitamin D. Thus the final link in the chain of evidence connecting the antirachitic effect of irradiating the body

¹ Bland-Sutton used cod-liver oil with success in preventing rickets in lion cubs at the London Zoo a number of years earlier.

surface and that resulting from the ingestion of certain foods was forged. Nevertheless, as a result of subsequent research it was concluded by Rosenheim and Webster and by Windaus and Hess (1927) that not cholesterol itself, but minute amounts of ergosterol with which it was contaminated were responsible for the antirachitic effects; ergosterol (of both animal and plant tissues) came to be regarded as *provitamin D* (see p. 651). Ergosterol, obtained from yeast, when irradiated yields a group of substances—*lumisterol*, *tachysterol*,² *calciferol* and *suprasterol*. During irradiation these products appear in the order given, but their proportions in the mixture at any moment depend upon the intensity and duration of the irradiation. Calciferol is not the end result, but at a certain stage the amount of calciferol formed is at a maximum beyond which it undergoes decomposition, and toxisterol is produced. This product of over-irradiation is highly toxic, having a very pro-

The ultraviolet rays effective in activating ergosterol are those which it absorbs, namely those with wave lengths between 250 and 313 $m\mu$. The maximum effect occurs at wave lengths around 280. Rays having wave lengths within this range falling upon the body surface are also effective in the prevention or cure of rickets. The antirachitic action common to irradiated foods and to direct irradiation of the body surface thus received, apparently, an essentially simple explanation, namely, that ergosterol, the provitamin, was transformed in either instance into vitamin D, which when taken in the food was absorbed from the gastro-intestinal tract and when formed in the skin was absorbed into the blood of the cutaneous vessels (see below).

The shortest rays from the sun which reach most localities of the earth have a wave length of about 290 $m\mu$, whereas those from artificial sources such as the carbon arc and mercury vapor lamp

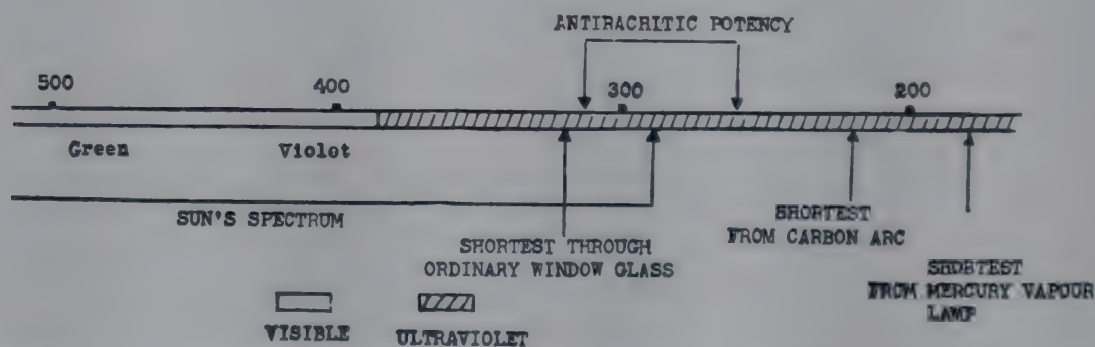


FIG. 253. Scheme of wave lengths of spectrum, showing the range of those possessing antirachitic properties. Figures refer to millimicrons. (Redrawn and modified from Blunt and Cowan.)

nounced effect upon calcium metabolism. Calciferol, which has the greatest antirachitic effect and comparatively little toxic action, is regarded as the pure vitamin and can be isolated in crystalline form from the other products. A daily dose of 0.0001 mg. of irradiated ergosterol is antirachitic for the rat; non-irradiated ergosterol is quite inactive. 0.025 micrograms (0.025 γ) of calciferol daily will prevent the development of rickets in a rat receiving a rickets-producing diet. The photochemical change involved in the activation of ergosterol is simply one of molecular rearrangement, non-irradiated ergosterol being isomeric with calciferol.

² Dihydratachysterol (referred to briefly as A.T. 10) is used therapeutically to raise the blood calcium in tetany. It has a relatively low antirachitic action, and its toxicity is higher than that of vitamin D.

³ Inhibition of such action, as shown by hypoprote thrombinemia, has been induced in rats upon diets deficient in vitamin K, by the oral administration of the bacteriostatic agent, sulfaguanidine (see p. 660).

are around 220³ and 180, respectively (fig. 253). Dust, smoke or water vapor in the atmosphere being opaque to the shorter waves markedly reduce the antirachitic effect of sunshine. Ordinary window glass filters out all rays shorter than 320 $m\mu$. Certain specially prepared types of glass are transparent to a proportion of the effective rays but sunshine transmitted through ordinary glass possesses no antirachitic action.

The antirachitic rays are incapable of penetrating the skin to any considerable extent beyond a depth of about half a millimeter or so. About 80 per cent of the rays with wave lengths between 250 and 300 $m\mu$ are absorbed or reflected from the corneous layer; the remainder are absorbed by the Malpighian layer and the corium. The blood in the capillaries of the corium acts as an effective filter, none of the ultraviolet rays penetrating beyond.

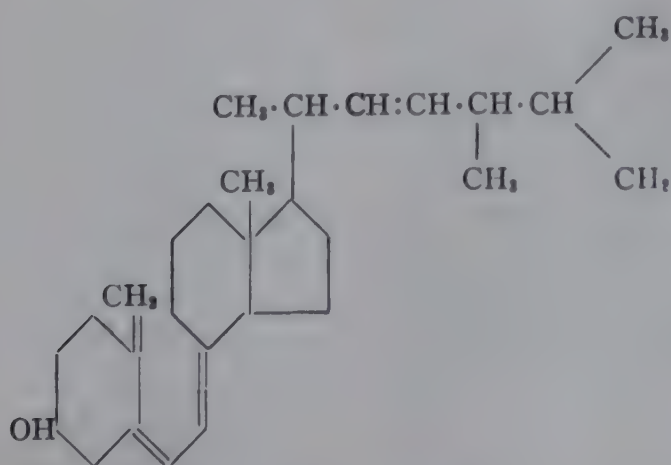
A very interesting observation made by Hou upon birds may be mentioned in this connection. He found that the preen gland (*glandula uropygialis*) serves an antirachitic function. This gland which is situated in the region of the tail feathers secretes an oily substance. During preening the secretion is distributed over the body feathers where it is activated by the rays of the sun. The irradiated material is either absorbed through the skin or obtained from the ingestion of feather particles in subsequent preening operations. Rickets is said to follow extirpation of the gland and is not cured by irradiation of the general body surface. Fur bearing animals probably obtain supplies of vitamin D in a similar manner, though the oily material is secreted not by a single structure but by glands distributed diffusely throughout the skin. The material which exudes becomes spread over the hairs and after irradiation either enters the body again through the skin or is acquired through licking the fur.

The conclusion of earlier workers mentioned on p. 649, namely, that ergosterol was the provitamin in animal skin, has had to be abandoned, for it has been shown that the vitamin D formed by the irradiation of ergosterol is not identical with that produced by irradiation of the skin. Waddell found that cholesterol after irradiation has an antirachitic potency, when tested upon chicks (see below) equal to that of cod-liver oil and therefore much greater than that of irradiated ergosterol. He concludes that the latter though it possesses a high antiarchitic power is not the vitamin D of cod-liver oil or of mammalian skin. In other words, the provitamin which is associated with cholesterol and which undergoes activation in the skin is some substance other than ergosterol. He points out that there is no direct evidence that ergosterol actually exists to any extent in animal tissues. Waddell's findings offer an explanation for certain discrepancies which have been noted in the past between the potencies of irradiated ergosterol and cod-liver oil. It had been recognized

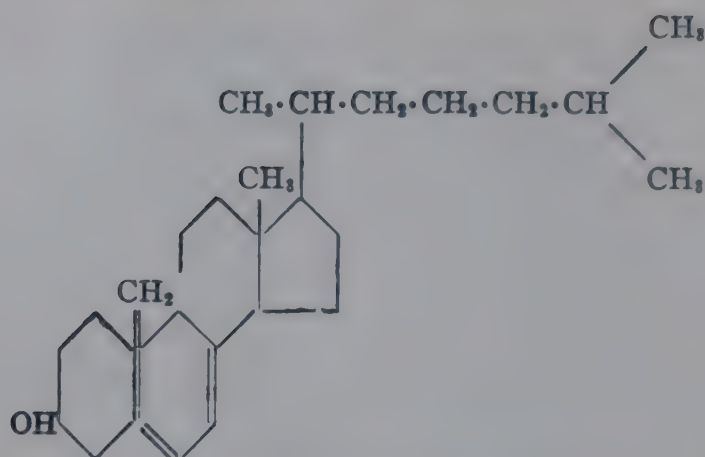
for example, that, per rat unit, cod-liver oil is more effective (about 30 times) than irradiated ergosterol in curing rachitic conditions in chicks. That is, an amount of irradiated ergosterol per gram of body weight which is adequate for the cure of rickets in the rat is inadequate for the chick. An amount of cod-liver oil, on the other hand, which is quite effective for the chick is inadequate for the rat. In the cure of human rickets, irradiated ergosterol in terms of rat units is less effective than is cod-liver oil. These facts had already led many to conclude that cod-liver oil and irradiated ergosterol contained different antirachitic substances. Irradiated cholesterol has also been reported to be more potent than irradiated ergosterol in curing infantile rickets. It has since been shown that 7-dehydrocholesterol present in small amounts in cholesterol is the provitamin of mammalian skin.

Calciferol, or vitamin D₂ as it is now called, an activated 7-dehydrocholesterol or vitamin D₃ (there is no vitamin D₁) are the two antirachitic vitamins of medical interest. The vitamin D produced by the irradiation of the skin or of milk and present in cod-liver oil is 7-dehydrocholesterol; that produced by the irradiation of yeast and which in oily solution has been marketed under various trade names (e.g., viosterol) is irradiated ergosterol (of yeast), i.e., vitamin D₂. Cows fed upon irradiated yeast simply transfer the vitamin to the milk which therefore owes its antirachitic properties to a vitamin different from that in irradiated milk. Several other antirachitic vitamins are known, some of which have been produced by the activation of provitamins prepared in the laboratory, while others are of natural occurrence, e.g., in the liver oils of different species of fish.

The formulae for calciferol and activated 7-dehydrocholesterol are shown below:



Calciferol (vitamin D₂)

Activated 7-dehydrocholesterol (vitamin D₃)

MAIN FOOD SOURCES OF VITAMIN D

Halibut liver oil is one of the richest natural sources of vitamin D. Cod-liver oil and the liver oils of bony fishes generally are other rich sources. Cod-liver oil, however, contains only 100 international units (p. 662) of vitamin D per gram as compared with 1200 units per gram in halibut liver oil. The liver oils of cartilaginous fishes are relatively poor in the antirachitic vitamin. Mammalian liver which is rich in vitamin A is poorly supplied with vitamin D. The cod and other larger fish receive their supplies of this vitamin, in part at least, from the bodies of the smaller fish upon which they feed. These in turn acquire it in a way similar to that in which they obtain vitamin A, i.e., from small plant-eating animal forms (zooplankton, p. 636) which are capable of synthesizing the vitamin. Bills concludes that the cod can also synthesize the vitamin. He does not believe it possible that the large stores of vitamin D in the liver of the cod can be derived solely from the food. That it is produced by the transformation of the provitamin in the fish's skin by radiant energy seems to be out of the question, the cod being a deep-sea fish.

Other animal sources of vitamin D are egg yolk, butter, cream and milk. The antirachitic potency of these dairy products is, as a rule, quite low and depends upon the vitamin D content of the diet and upon the extent to which the animal has been exposed to sunshine. Thus, summer butter is likely to have a higher antirachitic potency than butter produced in winter. Pasteurization does not lower the antirachitic property of milk. The egg yolk of irradiated hens or of hens receiving irradiated ergosterol has a high vitamin D potency. Small quantities of vitamin D are present in beef fat but not in lard.

Vegetable foods are, as a rule, very poor or lacking in this vitamin. It is absent from most vegetable oils (cottonseed, or maize oil) unless

these have been artificially irradiated. Green vegetables and fruits contain insignificant amount. Yeast has a high content of ergosterol and when irradiated acquires a high degree of antirachitic potency. The milk of cows fed upon irradiated yeast or milk after direct irradiation is also powerfully antirachitic.

An ordinary mixed diet is usually poorer in vitamin D than in any other vitamin; for this reason the diet of young children should be reinforced by this vitamin in some concentrated form. Adults probably receive all the vitamin D required in a well balanced diet.

THE EFFECTS OF VITAMIN D DEFICIENCY

Vitamin D is indispensable to the normal calcification of bone. Its absence from the diet is followed by the development of rickets in the young animal or of osteomalacia in the adult.

Infantile rickets (rachitis)

The fundamental feature of this disease is a disturbance of calcium-phosphorus metabolism with consequent defective ossification and the development of various deformities, e.g., *knock knees*, *bow legs*, *enlargement of the epiphyses*, *spinal curvature (scoliosis)*, *malformation of the chest*, *contracted pelvis*, *soft depressible areas in the parietal bones (cranio-tabes)* and the development of *bosses on the temporal bones* (see fig. 254). The natural curvatures of the long bones tend to become exaggerated. The enlargements of the costo-sternal junctions—"beading of the ribs"—causes a series of small swellings on either side of the thorax which is referred to as the "*rachitic rosary*." Dentition is usually delayed. Sweating of the scalp is common.

CHANGES IN BONE STRUCTURE:

The bones are relatively soft and pliable. *Defective calcification of the growing bone and compensatory hypertrophy of the epiphyseal cartilages* are the essential

pathological changes. A section of the epiphyseal junction of a *normal* growing bone shows the following zones in order from the free ends of the bone toward the shaft (fig. 283, p. 713).

- (a) A layer of resting *hyaline cartilage*.
- (b) A layer of *proliferating cartilage* in which the cells are arranged in regular columns paralleling the long axis of the bone.
- (c) A zone of *preparatory calcification*. The cells are still arranged in columns but deposition of calcium phosphate has occurred in the surrounding cartilaginous matrix.
- (d) A zone of *newly-formed bony trabeculae*—the spongiosa—produced through the invasion of the foregoing zone by osteoblasts derived from the periosteum. Marrow tissue fills in the spaces between the trabeculae.

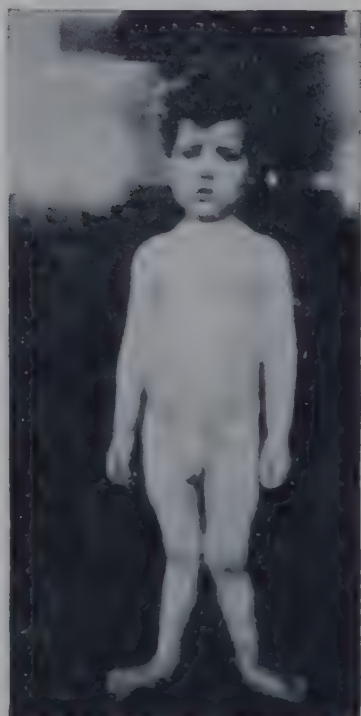


FIG. 254. Child aged 5 years with leg deformity caused by rickets. (After E. Mellanby.)

In a *rachitic bone* the layer of proliferating cartilage is greatly enlarged, being sometimes ten times its normal depth and the cells no longer show their regular columnar arrangement. This layer instead of being sharply demarcated from the zone of preparatory calcification sends finger-like cellular prolongations into the latter which is almost free from mineral deposit. The trabeculae are malformed and have lost their regularity of pattern. They are composed of *osteoid tissue*, i.e., a tissue very poor in or devoid of calcium. The cortex of the bone also may be partially replaced by osteoid tissue the extent to which this occurs varying with the severity of the disease (fig. 255).

On X-ray examination, the osseous abnormalities in a well-developed case of rickets are clearly evident. The entire shadow cast by the bone is less dense than normally and the ends of the bone are not sharply defined but have a "woolly" or

"moth-eaten" appearance (fig. 256). The articular ends also frequently show a concave (cupped) rather than a convex or straight contour. This appearance is due to the lack, or irregular distribution, of mineral in the zone of preparatory calcification. The latter normally presents a clearly defined almost straight band next to the unmineralized layer of proliferating cartilage.

Chemical analysis of the bones reveals a low mineral (Ca and P) content and a relative increase in organic matter and water. The ratio of ash to organic matter in normal, dry, fat-free bone is 3 to 2 whereas in rachitic bone it may be 1 to 2 or

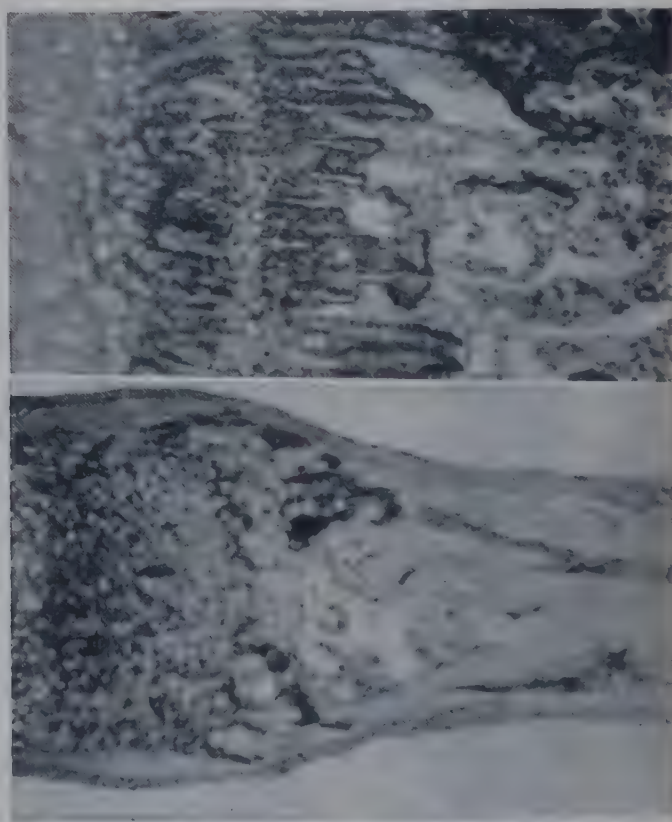


FIG. 255. Upper photograph, normal rib of rat. Rat weight 158 gm. 52 days on complete diet; continuous growth and gain in weight. Lower photograph. Thirty-four days on rickets-producing diet. Marked rachitic lesions. Note increased width and irregularity of proliferative cartilage, absence of calcium deposition, great excess of osteoid in region of metaphysis and about cortex. (After Hess.)

even 1 to 3. The normal Ca:P ratio remains unaltered (see also p. 712).

The inorganic phosphorus of the blood in rickets is lower than normal, i.e., below 3.0 mg. per 100 cc. (it may be as low as 1.0 mg.). This is an early sign. The serum calcium is usually normal unless the condition is complicated by tetany (p. 702). The plasma phosphatase is elevated several fold (Kay) above the normal value. In well-marked rickets the *intestinal contents* tend to become less acid in reaction, the stools which normally are slightly acid, neutral or slightly alkaline become definitely alkaline. Mineral retention is reduced

in the disease, i.e., the calcium and phosphorus balances (p. 711) show smaller positive values than the normal, or are negative.

THE RELATION OF CERTAIN FACTORS TO THE OCCURRENCE OF RICKETS:

(1) *Diet.* Vitamin D deficiency is the prime cause of human rickets, yet a very low intake of calcium or of phosphorus increases the susceptibility to the condition. The disease does not develop upon a minimal mineral intake provided that the vitamin D supply is abundant, nor will a diet high in the bone-forming minerals prevent the onset of rickets or arrest its course if vitamin D deficiency exists. Rickets, for example, may develop in an infant receiving cow's milk as its sole diet or even

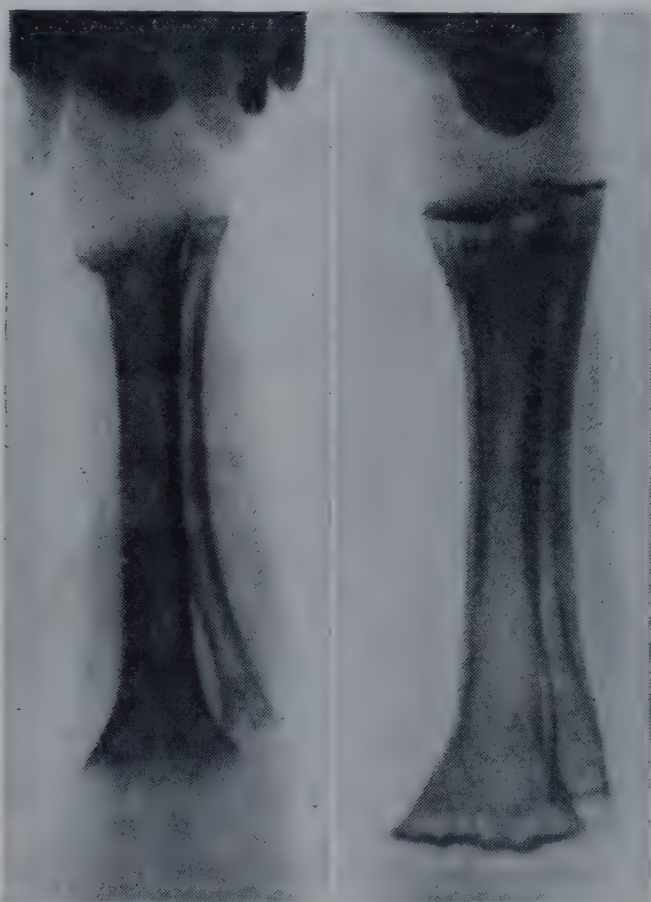


FIG. 256. Left hand photograph, rickety bone, tibia of child $1\frac{1}{2}$ years of age. Right, same bone after the child had received daily doses of cod-liver oil for a period of 14 days. (After H. A. Harris.)

when nursed at the breast if the mother's milk is lacking in the antirachitic vitamin. It may be mentioned here that, according to Hess, mother's milk is superior to cow's milk as a protection against rickets which cannot be explained either upon the basis of its mineral content (which is inferior in this regard to cow's milk) or upon its vitamin D potency.

A diet with a high proportion of cereal foods increases the susceptibility to rickets (see p. 656).

(2) *Age and rate of growth.* Rickets is a disease of the first two years of life, though the conditions known as *late rickets* and *osteomalacia*, which are essentially of the same nature, occur in later years (p. 656). The disease may commence a few weeks after birth. The period during which it most frequently makes its

appearance, however, is from the 3rd to the 10th month. It rarely commences after the second year, nor does it usually progress beyond this time, spontaneous healing taking place in the majority of cases around the 12th month. In some occasional instances the disease appears to commence in intra-uterine life—*fetal rickets*. *Premature infants* are highly susceptible to rickets. The possible reason for this is that since the fetus accumulates over 80 per cent of its calcium stores in the last 3 months of intra-uterine life those of the infant born before term are incomplete. Rapidly growing, overweight and apparently robust infants are more susceptible than others. Indeed Glisson (1660) to whom we owe the best classical description of the disease ascribed it primarily to over-nutrition. It was noted by Hess and his associates that rats in which growth was stimulated by a more abundant diet required a greater amount of irradiation to protect them against the disease than others upon the ordinary standard diet. McCollum and associates also found that healing was induced in rachitic rats by a 5-day period of starvation. Cretins, unless stimulated to normal growth by thyroid administration do not, it is said, become rachitic. The growth impulse, therefore, appears to be essential to the development of rickets.

(3) *Climate and season.* In the days before the use of antirachitic measures had become so general, the incidence of rickets was high in the large cities of northern latitudes and for the following reasons.

(a) There are fewer hours of sunshine annually than in southern localities. (b) The sunshine is less intense and the proportion of the shorter ultraviolet rays (300 to 290 m μ) is smaller than in southern climates. The two factors depend upon the sun's altitude—the nearer the sun is to the horizon the greater is the depth of the atmosphere intervening between it and the earth to act as a filter. Rickets is therefore more prevalent during the winter months when the sun reaches its lowest altitude; when this is below 35° the antirachitic effect of sunlight is almost negligible, since few rays shorter than 300 m μ reach the earth. In London and Glasgow which have been noted for their very high incidence of rickets the sun's altitude is less than 35° for 5 and 6 months of the year, respectively, whereas in such cities as Baltimore and Toronto which have shown a relatively low incidence of the disease, the altitude of the sun is less than 35° for only 3 and 4 months, respectively (fig. 257). In Jamaica and other southern localities the sun's altitude is never less than 50° and rickets is almost unknown. Also in temperate climates it is usual for rickets to become arrested during the summer months. A seasonal fluctuation in the blood inorganic phosphorus (low in winter and high in summer) has been found in infants living in temperate zones and appears to be a general phenomenon which again points to the climatic influence upon the susceptibility to rickets. Sunlight exerts its antirachitic effect not only through direct sunshine, but also by reflection from the sky ("sky shine") and from water, light-colored build-

gs, etc. Animals placed out of direct sunlight but exposed to a clear bright sky are protected from rickets. The atmosphere of large cities as a result of its content of smoke, dust and water vapor (humidity) is more opaque to the ultraviolet rays. (d) Children in temperate climates live a greater part of their time indoors during the winter months and expose less of their bodies when out of doors. Ordinary window glass, as will be recalled, is opaque to rays shorter than 320 mμ. Negro children living in temperate climates are

Experimental rickets and the discovery of the antirachitic properties of cod-liver oil

Mellanby produced rickets in puppies by placing them upon a diet of white bread and skim milk, i.e., one deficient in the only fat-soluble vitamin known at the time, namely, vitamin A (fig. 258). The diet included adequate amounts of vitamins B and C. He then showed that animals upon such a diet but receiving in addition cod-liver oil or

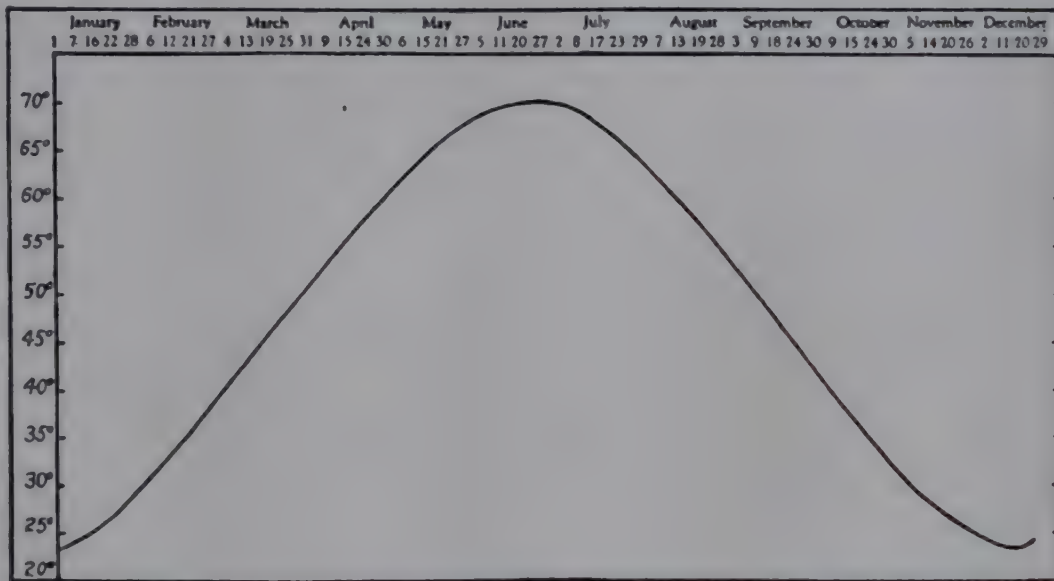


FIG. 257. Maximum daily altitude of the sun throughout the year at the latitude of Toronto. (From Tisdall and Brown.)



FIG. 258. A rickety dog. The animal was brought up on a diet deficient in the anti-rachitic vitamin D. (After E. Mellanby.)

especially susceptible to rickets because the skin pigment, which in their natural environment is a protection against excessive ultraviolet irradiation, further reduces the antirachitic effect of solar irradiation in northern latitudes.

There is no reliable evidence that the parathyroid glands or any of the other endocrines are concerned in the production of rickets.

butter (which were then known to be rich sources of vitamin A) developed normally. Linseed or olive oil was not protective. From these experiments the antirachitic property of cod-liver oil was definitely established. Mellanby concluded that vitamin A or a factor associated with it was the antirachitic factor. Experiments by others involving the investigation of the growth-promoting and antixerophthalmic properties of vitamin A aroused the suspicion that a second vitamin was present in cod-liver oil, butter, fat, etc., and that it, and not vitamin A, was the antirachitic factor. It was found for instance that rats on a diet containing 1 per cent of cod-liver oil thrived better than those on one with 20 per cent butter-fat. A much smaller quantity of butter-fat than this contains sufficient vitamin A for the prevention of xerophthalmia. A factor distinct from vitamin A, therefore, appeared to be lacking in butter. It was also observed that children receiving large quantities of milk (rich in vitamin A) sometimes developed rickets. McCollum and his associates furnished the final proof of the existence of two vitamins in cod-liver oil by subjecting this material to oxidation for from 12 to 20 hours. Oil so treated had no antixerophthalmic power (i.e., no vitamin A) but was powerfully antirachitic. He

proposed that this factor which was left undestroyed by oxidation should be called vitamin D. As confirmatory evidence of a separate antirachitic factor it was pointed out that coconut oil though containing no vitamin A furnished a certain protection against rickets. Moreover, it was shown by others that ultraviolet irradiation had no antixerophthalmic action.

Ca:P RATIOS IN THE EXPERIMENTAL PRODUCTION OF RICKETS:

The experimental animal employed most extensively for the study of rickets is the young (20-30 days) white rat. These animals unlike infants (p. 652) and puppies do not, as a rule, when deprived of vitamin D or sunlight develop rickets (though some reduction in bone mineral may occur) provided the diet is otherwise normal. If the vitamin D-free diet is also deficient in calcium or in phosphorus or the relative proportions of these are abnormal, rickets occurs. Unbalanced proportions of the bone forming minerals in the diet are of much greater importance than their absolute amounts. Thus a Ca:P ratio which is too high or too low though the actual amount of P or of Ca respectively is not reduced causes the disease, which can be arrested in turn by the administration of vitamin D or by ultraviolet irradiation. In puppies, and fowl, and apparently in the human subject, an improper balance of these minerals does not seem to be an important factor in the production of rickets. Rickets is also produced in the rat by the addition of magnesium or strontium carbonate to the diet. Beryllium carbonate also, when added in small quantities to a normal stock diet also produces bone lesions in this species similar to those of rickets. This condition is, uninfluenced however, by vitamin D administration.

THE ANTICALCIFYING EFFECT OF CEREALS. It had long been suspected that a high carbohydrate diet was conducive to the development of infantile rickets (p. 652). Mellanby showed the aggravating effect of cereals upon the development of canine rickets. Wheat germ and oatmeal were found to be especially potent in this regard. White flour, rice and other cereals had a less pronounced anticalcifying effect. There appears to be no relationship, however, between the rachitogenic action of these substances and their carbohydrate, protein or mineral contents. The anticalcifying effect is neutralized by vitamin D or by irradiating the cereal itself. The effect was also abolished by boiling the cereal with 1 per cent hydrochloric acid until all the carbohydrate had been converted to sugar. It is believed that Mellanby's results have an important bearing upon the development of human rickets; the influence of cereals upon dental caries is mentioned on page 658.

Mellanby concluded that cereals contained a factor for which the term *toxamine* was suggested. The removal of the toxic effect of the cereal by boiling with HCl was thought to be due to the destruction of this hypothetical substance. The results of the later experiments of Bruce and Callow provide the basis for quite a different explanation. The anticalcifying effect is not due to a toxic substance but to the fact that the phosphorus in such a cereal as oatmeal is in unavailable form, namely, inositolhexaphosphate or phytic acid. Phytic acid combines with calcium and magnesium forming the complex compound phytate. Boiling HCl hydrolyzes this compound, renders the phosphorus, calcium and magnesium available and favors calcification.

Late rickets and osteomalacia

Late or juvenile rickets is essentially the same as infantile rickets but occurs in older children—4 to 16 years. It is a rare condition in western civilization but is seen in India and is then due to the same causes as those which are responsible for the occurrence of osteomalacia. *Osteomalacia* is a failure of ossification of a nature fundamentally the same as that of infantile or late rickets but occurring in adults, especially women. Pathologically it is simply adult rickets. Nevertheless, the fact that it occurs after the period of growth and after puberty, pregnancy and lactation predisposes powerfully to it give it certain features which distinguish it from the infantile or juvenile type. The entire bone is softer than the ordinary ricket bone, its total mineral content being greatly reduced. The calcium shows a greater decrease than does the phosphorus, i.e., the Ca:P ratio is reduced. The magnesium content is increased. The blood calcium is lowered and tetany in consequence is a frequent complication. The calcium balance is negative, whereas the phosphorus balance is usually normal.

The softness and pliability of the bones leads to deformity sometimes of extreme degree. Pelvic abnormalities create serious hazards during childbirth. The disease is very rare in temperate climates though an outbreak occurred in Vienna following the first World War (hunger osteomalacia). Osteomalacia is common in India where the Mohammedan and high caste Hindu women follow the custom of purdah which demands that they live secluded within doors; they are thus deprived of the calcifying power of the sun's rays. The diet too is poor in meat, milk and vitamin D, but rich in cereals. The disease is also common in certain districts of China and is due to similar causes—a cereal diet combined with

in indoor life. Cod-liver oil or some other source of vitamin D is specific for the disease.

Celiac rickets

Celiac rickets is a condition of childhood associated with defective absorption of fat and calcium. As a consequence, fatty diarrhea, a negative calcium balance, low serum calcium, tetany, rarefaction of bone, skeletal deformities, anemia, and dwarfing occur. The condition responds to the administration of vitamin D. A similar condition occurs in adults and is then usually referred to as idiopathic steatorrhea or non-tropical sprue. The absorption of vitamin D is apparently defective in these conditions. The administration of vitamin D or exposure to ultraviolet light is sometimes of benefit.

THE MODE OF ACTION OF VITAMIN D

The precise manner in which vitamin D exerts its effect upon calcium and phosphorus metabolism is obscure. It has been supposed that one of its primary effects was to increase the absorption of these elements from the bowel. Evidence for increased calcium absorption has been afforded by studies of the calcium balance in rickets; irradiation with ultraviolet light or the administration of cod-liver oil converts a negative calcium balance into a positive one. Nevertheless, it would appear that the principal action of the vitamin is more probably the promotion of calcium and phosphorus deposition in the bones. Experiments with dogs given radioactive phosphorus support this conclusion. The toxic effects of the vitamin and its possible relationship to parathyroid function are dealt with in another place (p. 707).

THE RELATION OF VITAMINS A, C AND D TO DENTAL DISEASE

Vitamin A deficiency exhibits an effect upon the epithelium of the gums. In dogs upon A-deficient diets the stratified epithelium of the gingival margins becomes hyperplastic and irregular. In this state the gum readily becomes infected with microorganisms. These findings are clearly pertinent to periodontal disease (pyorrhea) in man. According to Howe, vitamin A deficiency also affects tooth structure, the odontoblasts laying down bone instead of dentine. The former tissue is softer and more porous than the latter. On the other hand, many question that vitamin A deficiency is a factor in the production of human caries. In the study of children, blind as a result of vitamin A deficiency, no evidence was obtained that the latter had an injurious effect upon the teeth.

Vitamin C. In scorbutic guinea-pigs and monkeys

marked changes in tooth structure occur, e.g., (a) disappearance of odontoblasts, (b) decalcification of the dentine which becomes porous, (c) disappearance of canals from the predentine, (d) dilatation of the vessels of the pulp, edema of the pulp tissue and lesions of its nerves. If vitamin C deficiency in man reaches the point where scurvy develops, marked changes in the gingival tissues comparable to those characteristic of the disease in guinea-pigs appear. According to Hanke, vitamin C deficiency in man of a milder degree than that which produces definite scorbutic manifestations may cause changes in the peridontal tissues, pyorrhea and caries. This conception, however, has

TABLE 64*

MODIFICATIONS OF BASAL DIET	AVERAGE NUMBER OF TEETH PER CHILD SHOWING INITIATION OR INCREASE IN CARIES	AVERAGE "DEGREE" OF INCREASE OF CARIES PER CHILD	AVERAGE AMOUNT OF "ARREST- ING" (HARDEN- ING) PER CHILD
1. Abundant fat-soluble vitamins as cod-liver oil added (no oatmeal).....	1.8	2.0	2.0
2. Intermediate amount of fat-soluble vitamins added (no oatmeal).....	3.0	4.0	1.2
3. Comparatively little fat-soluble vitamins (some oatmeal).....	5.8	6.7	0.04
4. Much vitamin D as irradiated ergosterol (basal diet).....	1.0	1.1	3.9
5. Cereal-free diet much vitamin D.....	0.37	0.32	4.7

* Modified M. R. C. Rep. 167.

not been adequately substantiated and the question of vitamin C deficiency in the etiology of ordinary dental caries is a matter for further investigation.

Vitamin D. M. Mellanby some years ago carried out a series of experiments in which the effect of vitamin D and other factors upon tooth structures were thoroughly investigated. Young puppies were fed upon vitamin D deficient diets for periods extending over several months. At the end of the experimental period the animals' teeth were carefully examined with regard to gross appearance and histological structure. The following defects were observed.

- (1) Delay in the eruption of the permanent teeth.

- (2) Thickening of the bony tissue of the jaws and irregularity in the arrangement of the teeth.
- (3) Poorly calcified enamel which showed pitting, grooving and pigmentation.

A diet of cereals—oatmeal, maize, white flour, rye or barley, especially the first of these, increased the severity of the defects. The anti-calcifying effect of cereals could be completely prevented by liberal allowances of cod-liver oil or irradiated ergosterol. Irradiation of the animals with the mercury vapor lamp exerted a less pronounced beneficial influence upon the tooth structure. Only slight benefit resulted from the addition of calcium to the vitamin D deficient diet, and perfect teeth were formed upon a low calcium intake provided that the allowance of cod-liver oil was liberal. On the other hand, when the vitamin D content of the diet was below the optimal value, calcium was found to enhance the beneficial effect. The addition of phosphorus to a diet either rich or deficient in vitamin D seemed to exert little effect upon tooth structure. These observations were taken to indicate that the mineral content of the diet was of minor importance as compared with the vitamin supply.

It was also shown that the teeth of the offspring were influenced by the diet of the mother during pregnancy. The deciduous teeth of puppies whose mothers during pregnancy and lactation had been fed diets deficient in vitamin D erupted late and were poorly calcified. The maternal influence was also seen in the permanent teeth, the latter being much less resistant to the ill effects of a deficient diet after weaning, if the puppies had been born of a mother which received a deficient diet during pregnancy and while she was suckling her pups.

Vitamin D was shown to have an important influence upon tooth repair in adult dogs. It is not possible to induce dental defects in full grown dogs by dietary means. When, however, a dog's tooth is filed at intervals of a few days it reacts to the injury by the formation of so-called secondary dentine. The amount and quantity of the new-formed dentine were found to be very favorably influenced by vitamin D administration; cereals were, on the other hand, detrimental. In none of the experiments upon puppies or adult dogs was actual caries produced. Yet, the effects upon tooth structure and repair resulting from vitamin D deficiency are undoubtedly pertinent to the question of the development of caries in man, since such defects would presumably prepare the way for bacterial invasion. In support of this assumption M. Mellanby has found from a histological examination of 1000 deciduous teeth and a large number of permanent teeth, that of those showing normal or nearly normal structure and good calcification 27 per cent showed carious cavities. Of teeth showing abnormal structure—hypoplastic teeth—85 per cent were carious. McCollum and his associates have also described "caries-like" lesions in rats fed upon low vitamin diets.

These observations conform with the trend of opinion

today, namely, that dental decay is due primarily to defect originating within the tooth itself rather than to local conditions within the mouth. The immediate cause of the erosion and decay of the tooth is, of course, bacterial invasion.

Direct evidence that the results of deficient diets are applicable to the question of human caries has been obtained by M. Mellanby. The results of investigations carried out upon English school children (6-10 years) are given in table 64.

The children were divided into groups. All received the same basal diet but the quantities of cereal and vitamin D were varied in the different groups. The teeth were examined and their state recorded at the beginning of the experimental period and again at the lapse of several months.

Taking the experimental results as a whole, the dietary factors influencing the development of caries, so far as this is the result of abnormalities of tooth structure may be summarized as follows, (a) the level of vitamin D intake or the degree of ultraviolet radiation (b) the proportion of cereal (anticalcifying) or the supply of calcium and phosphorus, though the latter factor would appear to be of secondary importance.

Tisdall and associates have obtained results which are, in the main, confirmatory of those of Mellanby. A definitely beneficial effect of vitamin D administration was demonstrated in children under the age of 10 years. The results obtained with older children were indecisive. Still more recent clinical research emphasizes the importance of vitamin D in the prevention of dental caries. In a group of school children given relatively large doses of vitamin D in the form of cod liver oil (800 units daily) over a period of eight months, dental caries was 65 per cent less than in the control group not receiving the vitamin. (McBeath and Verlin).

Some of the other conditions for which vitamin D has been advocated are, postoperative tetany, chronic arthritis, psoriasis and acne. In some of these conditions massive doses were used (up to 500,000 units) at a single dose. Such unphysiological dosage is not free from danger (p. 708).

VITAMIN E (ANTI-STERILITY)

Mattill and Conklin observed some years ago that rats reared upon a diet of whole milk were usually sterile. Evans and Bishop observed a failure of reproduction in rats (male or female), fed upon a diet consisting of casein, starch and lard and containing butter fat or cod-liver oil as well as the other known vitamins and essential minerals. The addition to the diet of lettuce, wheat germ, or alfalfa corrected the defect. It was therefore concluded that a hitherto unknown vitamin existed which was necessary for normal reproduction. This was termed vitamin E.

In male rats on a vitamin E deficient diet the loss of fertility is a progressive process. In the earlier stages of the vitamin deficiency the spermatozoa lose their motility; later they fail to be produced. Finally the spermatogenic epithelium degenerates and the sex instinct fails. In females, estrus occurs normally and when fertilization occurs the implantation of the ovum is not prevented but the embryos after developing for a short time die and are resorbed. The nature of the defect in embryological development leading to fetal death has been studied by Adamstone in chick embryos and hens on vitamin E deficient diets. He found that cell proliferation in the mesoderm forms a ring at the blastoderm stage which by strangling the blood vessels cuts the embryo off from its blood supply. Rarefaction of the mesenchyme and failure in the development of the blood-forming tissues is the principle abnormality seen in the embryos of vitamin E deficient rats.

In animals the administration of vitamin E, so it is claimed, even in the absence of any obvious deficiency, exerts an effect upon the reproductive functions. For example, wheat germ oil fed to rabbits is said to increase the size of the litters, and it has been asserted that cows previously sterile have passed through normal pregnancies after receiving large doses of vitamin E. Several observations point to vitamin E as playing an essential rôle in the metabolism of skeletal muscle, but though α -tocopherol is curative for the nutritional muscular dystrophy of rabbits, its administration in human neuromuscular disorders has not proved of benefit. Indeed, there is no proof that any clinical condition is due to a deficiency of this vitamin. Though earlier reports seemed to indicate that vitamin E in the form of wheat germ oil was of value in the treatment of sterility in women due to repeated miscarriages (habitual abortion), and though some support for such an action has been given by more recent work, full confirmation has not been secured. It does appear, however, that many pregnant women suffer from a deficiency of vitamin E.

It has been shown by Evans and his associates that vitamin E, or a principle closely related to it, has also a growth promoting action upon rats after the fourth month. The influence upon growth is not secondary to an effect of the vitamin upon the sex glands since it is evident after the latter have been removed. Other manifestations of vitamin E deficiency in rats are partial paralysis of the hind limbs, due to degenerative changes in the muscles, and loss of hair. These appear only

after a prolonged period (15 months) on diets low in vitamin E.

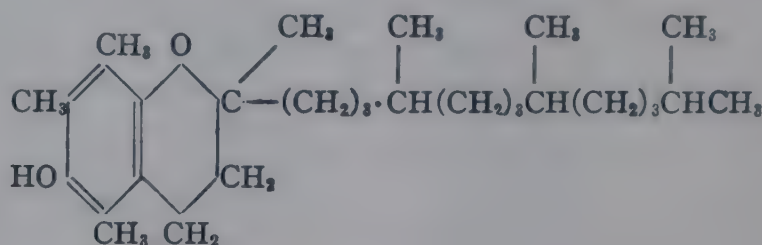
There appears to be a relationship between the pituitary and the thyroid and vitamin E. The potency of extracts of pituitaries of female rats on vitamin E deficient diets to induce ovulation in rabbits is reduced; the power is restored by the administration of vitamin E. Degenerative changes in the pituitary, involving both acidophil and basophil cells, have been described as resulting from a deficiency of this vitamin.

Chemical properties and sources

Vitamin E is soluble in fat and in the usual fat solvents. As in the case of the other fat-soluble vitamins D and K and carotene, bile in the intestine is necessary for its absorption. Its chief sources are green vegetables, e.g., lettuce, peas, alfalfa and the germ of various seeds. Wheat germ oil has a very high vitamin E potency and most ordinary vegetable oils contain it in fairly large amounts. It is absent from the endosperm of wheat (white flour).

Vitamin E is a higher alcohol with the formula $C_{29}H_{50}O_2$. It is not a single compound but like vitamin D is multiple in nature, the different compounds with vitamin E activity being known as *tocopherols* (tokos = childbirth, phero = I bear). Three physiologically active, crystalline isomeric compounds—*alpha*, *beta* and *gamma tocopherols*—have been obtained by Evans and his associates from vitamin E concentrates of wheat germ oil. α -tocopherol, which alone is present in lettuce oil, has much the highest potency of the three. The tocopherols are associated in nature with anti-oxidative agents, i.e., substances which inhibit the oxidation and consequent rancidity of certain oils and fats. This antioxidative property of substances rich in vitamin E does not run parallel with their biological activity so is apparently not due to vitamin E itself. Vitamin E is very susceptible to oxidation and rapidly loses its activity in the presence of fats and oils undergoing oxidation, a fact which is made use of in preparing E-deficient diets, an oil or fat such as cod-liver oil or lard on the verge of rancidity being added in order to destroy the last trace of vitamin E activity. From their antioxidative properties and the similarity of their absorption spectra it was suspected that tocopherols and hydroquinone were closely related chemically. This suspicion was substantiated by the identification by Fernholtz of durohydroquinone among the decomposition products of α -tocopherol when subjected to heat. α -tocopherol was later synthesized by Karrer and his colleagues,

and by Smith, Ungnade and Pritchard from trimethylhydroquinone and phytylbromide. The following structural formula has been proposed for it by Fernholtz:



α -tocopherol

The effect of vitamin E in enhancing the action of vitamin A has been mentioned (p. 636).

VITAMIN K, THE ANTIHEMORRHAGIC OR COAGULATION VITAMIN

Chicks, young geese and ducklings upon diets lacking in green stuff are subject to a fatal hemorrhagic disease which, as a result of the work of Dam and his associates, has been shown to be due to vitamin K deficiency. It has been established by these and other workers that the bleedings are due to a reduction in the prothrombin concentration of the blood (see p. 91). The low value of this essential factor in the clotting mechanism leads to a prolonged coagulation time. Green leaves, especially alfalfa and other clovers, spinach, cauliflower and cabbage, are rich sources of vitamin K; cereals, carrots, yeast and wheat germ contain it in minimal amounts, while little or none is present in potatoes, mangolds or cod-liver oil.

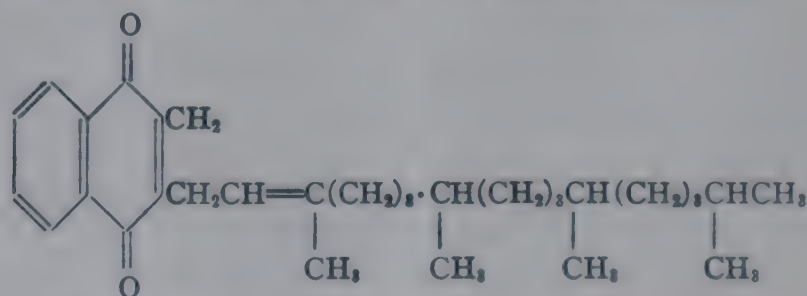
It has not been found possible to induce a hemorrhagic tendency in any mammal so far investigated—guinea pigs, rats, hogs or dogs—by feeding K-free diets alone. No hemorrhagic disease in man, so far as is known, is due to lack of

degree than occurs in the intestines of birds; or better absorption. Bile, as shown by Grea and Schmidt, is necessary for the absorption of vitamin; in animals with bile fistulae and in

structive jaundice in man, failure of the vitamin to be absorbed is the cause of the bleeding tendency associated with these conditions. The administration of vitamin K concentrates combined with bile salts is corrective (see also p. 466). Not only obstructive jaundice but any condition which interferes with the absorption or utilization of the vitamin may result in K deficiency and a tendency to bleed. Thus in sprue and other states associated with defective fat digestion and absorption in biliary or gastrocolic fistula or in some liver diseases, vitamin K lack may be encountered. The hypoprothrombinemia induced by dicumarol (p. 90) or by salicylic acid, and the hemorrhagic tendency of the new-born are counteracted by the administration of vitamin K.

Chemistry

McKee and his associates in 1939 isolated vitamin K from alfalfa (called K_1) and from putrefying fish meal (K_2). Later K_1 was synthesized by Binkley and by Fieser and their associates. It is 2-methyl-3-phytyl-1,4-naphthoquinone and has the following formula.



Vitamin K_1 (2-methyl-3 phytyl-1, 4-naphthoquinone)

vitamin K in the diet. Almquist and Stockstad have shown that some synthesis occurs in the intestine of chicks as a result of bacterial action,³ and it seems established that the immunity of man and other mammals listed above to a dietary lack of vitamin K is due either to synthesis in greater

Vitamin K_1 is fat-soluble; it is contained in the unsaponifiable fraction of the alfalfa lipids. Vitamin K_2 is similar chemically and in its physiological action to K_1 but possesses only 60 per cent of the latter's potency. Several other naphthoquinone compounds have been shown to possess vitamin K activity. One of these was isolated in 1933 by

³ For footnote see page 650.

Anderson and Newman from tubercle bacilli and later synthesized, but it was not until 1939 that its antihemorrhagic property was demonstrated by Almquist and Klose. This substance (sometimes called phthiocol) is 2-methyl-3-hydroxy-1,4-naphthoquinone. Other naphthoquinone compounds have since been investigated. Of these 2-methyl-4-naphthoquinone is the most powerful anti-hemorrhagic factor known, being two or three times more potent than K_1 . It differs from the latter chemically only in that it does not contain the phytyl group; the latter would appear therefore to be of no importance in so far as physiological activity is concerned. Water-soluble synthetic naphthoquinone derivatives have been prepared. Some of these can be given orally without bile salts or intravenously, which of course is a decided advantage.

THE MEASUREMENT AND STANDARDIZATION OF VITAMIN POTENCIES

The general principle employed in testing a food material for its content in a given vitamin is as follows. An animal e.g., rat, guinea-pig, etc., susceptible to deprivation of the vitamin to be tested is placed upon a diet which lacks that vitamin but is otherwise adequate. The substance containing the vitamin is added to this basal diet and the amount which is required to prevent the appearance of the effects characteristic of a lack of the vitamin under test (preventive test) or the amount required to correct the effect after it has appeared (curative test) is noted. In most cases the preventive test is employed. The minimal daily quantity of the food material required is said to contain 1 unit of the vitamin. For example, in testing vitamin A, a group of young (21–29 days old) healthy rats are placed upon a diet of purified casein, cornstarch and containing suitable amounts of brewer's yeast to furnish vitamins B_1 and B_2 and of irradiated ergosterol as a source of vitamin D. A suitable amount of a mixture containing the essential minerals Ca, P, K, Na and Fe, is added. Vitamin A is completely excluded. Another group of rats is placed upon this diet but containing, in addition, weighed amounts of the food to be tested, e.g., butter, fat, green vegetable or other material. After a short time (4 weeks or so) growth ceases in the first group of rats and the first eye symptoms appear. The minimal quantity of material required to be fed to the second group for the prevention of these effects and to cause a gain in growth of 3 grams per week is said to contain 1 unit of vitamin A. The content of vitamin A in the various foods may therefore be expressed as the number of units per gram, per ounce or per pound; or per 100 calories. Thus, a good sample of butter contains about 22,500 units per pound and 700 units per 100 calories, whereas lettuce contains

only 2400 units per pound but on account of its low calorie value, some 2775 units per 100 calories. Similar methods are employed for the measurement of the vitamins B_1 , C, D and E. The prevention of arrested growth being the criterion used for estimating B_1 , the prevention of scurvy in guinea pigs the criterion for C and for vitamin E the power to restore fertility in a female rat in which a series of previous resorptions has occurred. In the measurement of vitamin D, young rats (40–70 grams in weight) are deprived of ultraviolet irradiation and placed for 3 or 4 weeks upon a special rickets-producing diet, i.e., one with a high Ca:P ratio⁴ and lacking in the antirachitic vitamin. A unit of vitamin D is taken as the daily amount which will prevent (preventive test) or will cure the condition after it has appeared (curative test). Evidence of the

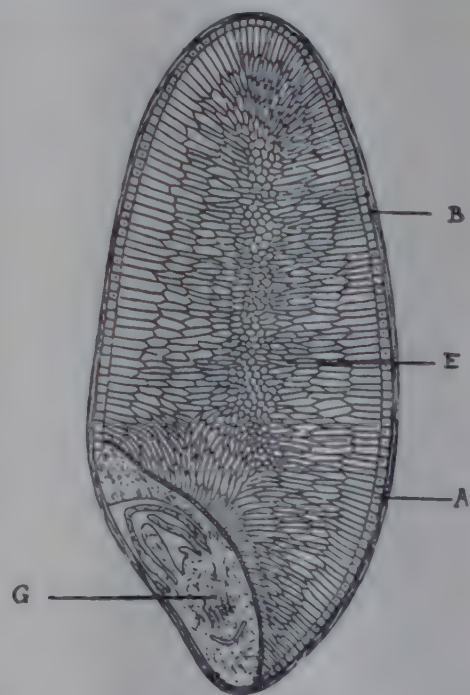


FIG. 259. Diagram of a longitudinal section through a grain of wheat, showing B pericarp, forming the branny envelope; A, aleurone layer of cells forming the outermost layer of the endosperm removed with the pericarp during milling; E, parenchymatous cells of the endosperm; G, embryo or germ. (From *Med. Res. Council Rep.* 1932, No. 167.)

existence and extent of the disease or of the degree of healing is obtained by (a) X-ray examination, (b) analysis of the bones of their ash content or (c) by means of the "line test." Determination of the ash content or examination of the bone by means of the line test involves the sacrifice of the animal, the former method being used in the preventive test, the latter in the curative test. By X-ray examination the extent of healing under vitamin D administration can be followed in the same animal. It may be used either in a preventive or a curative test.

⁴ Steenbock's rachitogenic diet is as follows:

	%
Ground yellow maize.....	76
Wheat gluten.....	20
Sodium chloride.....	1
Calcium carbonate.....	3

Its Ca:P ratio is 4 to 1.

The "line test" depends upon the fact already alluded to p. 653 that the end of the severely rachitic bone is mineral-free. When healing commences lime salts are deposited. In the employment of this test the animals are kept upon a rachitogenic diet until severe rickets has developed. A measured dose of the material containing vitamin D is then administered daily. At the end of 10 days the animals are killed and the ends of the tibiae are split longitudinally and immersed in a 1.5 per cent solution of silver nitrate. If calcium phosphate is present in the metaphysis of the bone, silver phosphate is formed which upon exposure to light is reduced to metallic silver which causes a dark band to appear; the test is then designated as "positive" (+). In the absence of healing the bone end remains unchanged in color; the test is then said to be "negative" (-). The degree of healing may be gauged from the depth of the darkened band, and is usually expressed by the signs +, ++ or +++. A colorimetric method for the determination of vitamin D can be employed. The reagent is antimony trichloride and acetylchloride in chloroform. It reacts with the vitamin to give a yellowish pink color.

Riboflavin possesses the property of fluorescence. Upon this is based the fluorometric method of assay, the estimation being made upon solutions of the vitamin by means of a fluorophotometer. An animal assay method, based upon the general principles outlined above, or a microbiological method, is also available. The growth response to the vitamin of *Lactobacillus casei* is the basis of the latter method. For the assay of *nicotinic acid* either a colorimetric or a microbiological method may be used. The former method is based upon the yellow color produced by the reaction of pyridine with an aromatic amine in the presence of cyanogen bromide. The microbiological method depends upon the effect of nicotinic acid upon the growth of cultures of the dysentery bacillus. A colorimetric and a microbiological method are also available for assaying *pyridoxin*. The colorimetric method is based upon the color which appears when pyridoxin is acted upon by diazotized sulphanilic acid and p-nitroaniline in an alkaline medium. The microbiological method employs the fact that yeast cells or lactic acid bacilli grow only in the presence of pyridoxin. A rat growth method can also be used, in which rats are fed a basal diet complete in all respects except that it lacks pyridoxin. Other methods of pyridoxin assay are the curative and preventive methods based upon the development of acrodynia in rats. *Pantothenic acid* may be assayed by the chick-growth test or by the growth response of certain bacteria, e.g., *Proteus morganii* or *Lactobacillus casei*.

A reliable chemical method has been developed for the assay of vitamin C, based upon its high reducing power. The vitamin C content of a material is es-

timated from the reduction (decoloration) of the 2,6-dichlorophenolindophenol. For the detection of vitamin C deficiency clinically either the capillary sistance test (p. 95) or the intradermal test may be used. The intradermal test consists of injecting a solution of 0.0025 M dichlorophenolindophenol. The dye is decolorized in 10 minutes in subjects well supplied with vitamin C but not for 13 minutes or more in those suffering from a deficiency of vitamin C. The vitamin concentration of the plasma also may be employed in the saturation test (pp. 647 and 648).

Vitamin K may be assayed by the curative method of Almquist and Klose. This is based upon the fact that the clotting time of vitamin K deficient chicks becomes normal within three days after their being placed upon an adequate diet.

Owing to the confusion which has arisen from the employment by various workers of different standards for measuring and expressing vitamin potencies the Commission on Biological Standardization of the League of Nations has recommended the following vitamin units for international usage.

- (1) Vitamin A unit = The vitamin A activity of 0.6 microgram (0.6 γ) of pure β -carotene prepared from carrots by Willstätter's method. (This is from $\frac{1}{10}$ the amount required daily to cure xerophthalmia and restore growth in the rat.)
- (2) Vitamin B₁ unit = The antineuritic activity of 10 mg. of a standard adsorption product of the vitamin prepared from an extract of rice polishings. Twenty to thirty mg. daily of this preparation will cure polyneuritis in a pigeon (300 grams) on a diet of polished rice.
- (3) Vitamin C unit = The vitamin C activity of 0.05 cc. l-ascorbic acid. This is about $\frac{1}{10}$ the quantity required daily to prevent scurvy in a guinea-pig on a scorbutic diet.
- (4) Vitamin D unit = Antirachitic activity of 0.025 microgram (0.025 γ) of crystalline vitamin D (calciferol). This amount given daily for 8 days to a rachitic rat causes a broad band of calcification in the metaphysis of the proximal end of the tibiae.

CHAPTER LVII

DIETARY REQUIREMENTS

In planning a diet the following requirements must be taken into account.

- (1) The total caloric value.
- (2) The proportion of the different foodstuffs—carbohydrate, fats, and protein.
- (3) The mineral constituents.
- (4) The vitamin content.

In order that the body shall not be forced to consume its own tissues for fuel, the caloric value of the ingested food for 24 hours must balance the heat eliminated by the individual during the same period. The basis for computing the latter value is the basal metabolic rate plus an allowance for the energy expended in performing work. The basal metabolic rate is obtained by direct determination (p. 533) or by calculation from the subject's height and weight (p. 534).

The following table gives the average extra caloric allowances for different grades of muscular activity:

	Calories
Sedentary life.....	800- 900
Light work, e.g., professional and business men.....	900-1400
Moderate work, e.g., mechanics.....	1400-1800
Heavy work, e.g., laborers, athletes, etc.....	1800-3500

SAMPLE CALCULATION OF CALORIC REQUIREMENT.

A young average-sized man (surface area 1.8 square meters) has a basal metabolism of $(1.8 \times 40 =) 72$ calories per hour, or a total of $(72 \times 10 =) 1152$ calories for the 16 hours that he is awake. During sleep the metabolism is 90 per cent of the basal value. So $(\frac{90}{100} \times 72 \times 8 =) 518$ Calories would be his energy requirement for 8 hours of the day. Apart from that required for work his total daily requirement is therefore $(1152 + 518 =) 1670$ Calories. To this is added the appropriate work allowance given in the table above which will bring the total up to from 2500 to over 5000 calories. An allowance of 6-7 per cent is made to cover the increased metabolism due to the food itself (specific dynamic action, p. 554). These calculations are given in tabular form below.

	Calories
Basal metabolism (16 hours).....	1152
Metabolism of sleep (8 hours).....	518
Allowance for light work.....	1200
	2870
6 per cent for S.D.A.....	172
Total.....	3042

The actual caloric values of various foodstuffs are given in table 65. See also table 45, p. 536, for the energy requirements for different types of exercise. The effect of climate upon the metabolism must also be taken into account, a higher energy intake being required in cold and temperate climates than in the tropics.

THE RELATION OF AGE AND SEX TO THE CALORIC REQUIREMENT

Women have a somewhat lower basal metabolic rate (p. 534) than men and generally speaking they expend less energy in muscular work; their food requirement is proportionately less.

Children require weight for weight a greater food allowance than the average adult for three reasons. (a) Their basal metabolic rate is considerably higher especially at the younger ages. (b) A proportion of the food material is utilized for building body tissue. (c) Children, as a rule, expend more energy in muscular activity than the average adult. For example, a boy of 16 years of age, of average physique and taking an active part in games requires a daily energy intake equal to that of a man—from 3000 to 4000 Calories or from 50 to 70 Calories per kilogram of body weight per day (average adult requirement 46 Calories per kilogram). When growth is very rapid an even larger allowance may be required. The food requirement of a girl of from 16 to 18 years of age is approximately that of a full-grown woman though of course size, rate of growth and the amount of exercise which she takes are modifying factors. During the first two years of life the daily dietary requirement amounts to about 100 Calories per kilogram (45 Calories per pound) of body weight and from the second to the fourteenth year to about 80 Calories per kilogram.

The relative caloric requirements at different ages are shown in table 66, the requirement of the average man, i.e., one having an energy expenditure of 3000 Calories being taken as unity. In computing the food requirements of a household this is referred to as the "man value." As a first approximation the other members of the family are apportioned calorie allowances in accordance with the figures shown in the table. Thus, the mother's allowance would be 0.83 of a "man value"

TABLE 65

Average composition and energy values of edible portions of some common food materials

	PER CENT					ENERGY VALUE	
	Water	Protein N × 6.25	Fat	Carbo- hydrate	Ash	Per kg.	Per pound
	grams	grams	grams	grams	grams	calories	calories
Meat:							
Beef, round steak, medium fat.....	54.8	23.5	20.4	1.2	2,860	1,300
Mutton, leg roast.....	50.9	25.0	22.6	1.2	3,125	1,420
Pork, ham, luncheon bacon, side.....	49.2	22.5	21.0	5.8	2,870	1,305
	18.8	9.9	67.4	4.4	6,665	3,030
Chicken:							
Broilers.....	74.8	21.5	2.5	1.1	1,110	505
Fish, cod, whole.....							
Herring, whole.....	82.6	16.5	0.4	1.2	715	325
Salmon, whole.....	72.5	19.5	7.1	1.5	1,455	660
Trout, brook, whole.....	64.6	22.0	12.8	1.4	2,090	950
	77.8	19.2	2.1	1.2	980	445
Fats:							
Butter.....	11.0	1.0	85.0	3.0	7,930	3,605
Lard.....			100.0		9,285	4,220
Suet.....	13.7	4.7	81.8	0.3	7,790	3,540
Cheese:							
American, red.....	28.6	29.6	38.3	3.5	4,765	2,165
Milk.....	87.0	3.3	4.0	5.0	0.7	715	325
Eggs, hens', boiled.....	73.2	13.2	12.0	0.8	1,685	765
Flour, white, wheat.....	11.5	11.4	1.0	75.6	0.5	3,650	1,660
Bread, white.....	35.6	9.3	1.2	52.7	1.2	2,650	1,205
Fruit:							
Apples.....	84.6	0.4	0.5	14.2	0.3	640	290
Banana.....	75.3	1.3	0.6	22.0	0.8	1,010	460
Cherries.....	80.9	1.0	0.8	16.7	0.6	805	365
Grape fruit.....	93.6	0.6	0.1	5.7	267	120
Oranges.....	86.9	0.8	0.2	11.6	0.5	528	240
Vegetables:							
Beans, dried.....	12.6	22.5	1.8	59.6	3.5	3,530	1,605
Cabbage.....	91.5	1.6	0.3	5.6	1.0	320	145
Lettuce.....	94.7	1.2	0.3	2.9	0.9	206	90
Potatoes.....	75.5	2.5	0.1	20.9	1.0	968	440
Sugar, granulated.....				100.0	4,090	1,860
Chocolate.....	5.9	12.9	48.7	30.3	2.2	6,295	2,860
Cocoa, powder.....	4.6	21.6	28.9	37.7	7.2	5,105	2,320

(Taken for the most part from Bulletin 28, Revised Edition, U. S. Department of Agriculture, 1906, by W. C. Atwater and A. P. Bryant.)

TABLE 66

Scale of food requirement (Calories) based upon the adult male standard of 3000 Calories per day (After Cathcart and Murray)

Man.....	1.00
Woman	0.83
Boy 14 up.....	1.00
Girl 14 up.....	0.83
Child 12 to 13½.....	0.90
Child 10 to 11½.....	0.80
Child 8 to 9½.....	0.70
Child 6 to 7½.....	0.60
Child 3 to 5½.....	0.50
Child 2 to 2½.....	0.40
Child 1 to 1½.....	0.30
Child up to 1.....	0.20

about 2500 calories, whereas a boy of 14 years of age would receive 3000 Calories.

THE PROPER PROPORTIONS OF THE THREE FOOD-STUFFS IN AN ADULT DIET

In a diet having a total energy value of about 3000 calories the amounts and percentages of its three main constituents are as follows.

	GRAMS	CALORIES	PER CENT OF TOTAL CALORIES, APPROXIMATE
Carbohydrate.....	380	1440	48
Fat.....	133	1200	40
Protein.....	90	360	12

Cereals and other carbohydrate foods contain a large proportion of water. Lean meat is about 75 per cent water, whereas fats and oils are highly concentrated foods, being for the most part water free. It will also be recalled that weight for weight fat has more than double the caloric value than that of pure carbohydrate or protein. Over 70 per cent of the protein intake of the adult should be made up of proteins of first class biological value (p. 559). In the diets of persons living in northern climates the calories derived from fat may constitute 45 per cent or more of the total.

The protein allowance

A great deal of controversy has centered around the question of the protein requirement of the adult. Chittenden some years ago made a study of the subject in a series of experiments upon himself and groups of students, soldiers and athletes. He showed that nitrogen equilibrium

could be maintained upon a total daily intake of 25 grams or less of first class protein.¹ Upon an ordinary mixed diet containing proteins of varying biological values nitrogen equilibrium was established on an allowance of between 40 and 50 grams for a man of average weight (70 kgm.). This is from 0.6 to 0.7 grams of protein per kilogram. Chittenden claimed that the larger protein intake of 120 grams considered by previous observers (e.g., Voit) were unnecessary, if not actually deleterious to health. It was contended that the renal work entailed in the excretion of large quantities of nitrogen was conducive to kidney disease. Many other ills were ascribed to the excessive consumption of protein. He also reduced the total energy intake to around 2000 calories and stated that the more liberal diets were dictated by appetite rather than by physiological necessity. His subjects, he claimed, could carry out their usual activities just as well upon such a diet and enjoyed better health than they had, previously, upon their customary fare.

Since nitrogen equilibrium can be established upon a protein intake of around 40 grams per day, it would seem unnecessary to give more. The excess amount must obviously be catabolized to furnish energy, which can be furnished more economically by non-nitrogenous food, or be simply stored as carbohydrate or fat. The weak point in this argument is, as many critics of the low protein dietary have pointed out, that the ability of the body to adapt itself for a few months to a restricted protein intake is not proof that such constitutes the physiological optimum. It has also been pointed out that custom has dictated for persons in temperate climates a higher protein intake than Chittenden's standard. Pearl has estimated that the average daily protein intake per person of the population of the United States is around 120 grams. Even the diets of the Japanese and of the hardier races of India, according to McCay, contain a greater quantity of protein than that recommended by Chittenden. McCay observes that tribes in India who are accustomed to diets with the higher protein content are healthier and of better physique than those subsisting upon a more restricted protein intake. The investigation of Orr and Gilks also seems to show clearly the value of a generous protein allowance. Their report is based upon a study of two African tribes, the

¹ We have already seen that the daily urinary excretion of N on a nitrogen-free diet but of adequate calorie value is around 3 grams (p. 552). This represents the catabolism of 18.75 grams (3 x 6.25) of tissue protein.

Masai and the Akikuyu, who though living side by side eat quite different diets. The diet of the Masai has a high protein content; it consists largely of meat, milk and blood. They obtain the latter from the living animal by piercing its jugular vein with an arrow. The Akikuyu live upon a vegetarian diet composed of cereals (chiefly maize) legumes, plantains, sweet potatoes and other tubers, and green leaves. The members of the meat-eating tribe are some 5 inches taller and 50 pounds heavier than the vegetarians, and their muscular power is about 50 per cent greater. The Masai are comparatively free from disease, whereas bone deformities, dental caries, anemia, pulmonary diseases and tropical ulcer are prevalent among the Akikuyu. Arthritis, however, was found to be much more common among the Masai. Though these tribes come of different original stocks there is a considerable amount of intermarriage, and the differences between them in physique and health appear to have a dietary rather than a racial basis.

Such facts suggest that, in furthering the well-being of the body, protein probably plays an important part which is not revealed by short term experiments based upon the study of nitrogen balances. There are indications that physical fitness and resistance to disease are associated with the higher protein intakes. It may be that it is only by supplying a comparatively large quantity of protein in the diet that certain vital tissues, e.g., ductless glands, can obtain adequate amounts of essential amino-acids to carry out their functions at the highest state of efficiency. There is little evidence, on the other hand, that a high consumption of protein causes renal or other diseases. Thomas records that the Greenland Eskimos are almost exclusively carnivorous, consuming enormous quantities of meat (and fat) yet renal and cardiovascular disease is not common among them.

However, it has been shown by Smadel and Farr that the level of protein in the diet of rats has a pronounced influence upon the course of experimental nephritis. In animals upon a low (5 per cent) protein diet the disease ran a much more favorable course than in those upon a diet containing a large proportion of protein (40 per cent). Nephritis in animals has also been reported to follow very high protein intakes, but the levels are far above anything possible in human dietaries.

It now appears that the true protein requirement for the average man lies about mid-way between the two extremes of Chittenden and the older observers. This is from 70 to 100 grams,

i.e., somewhat more than 1 gram per kilogram body weight. In an extensive investigation carried on over a period of six years upon some 400 medical students living on diets of their own choice, Beard found that the average daily excretion of nitrogen in the urine was about 11 grams. This (after allowance was made for the loss of nitrogen in the feces) was calculated to represent the consumption of approximately 77 grams of protein, i.e., approximately 1.1 gram per kilogram. In a nutrition survey in a suburb of Toronto undertaken by Ferguson and McHenry upon a large number of school children, the daily consumption of protein was 75 grams for girls aged from 16 to 20 years, and 100 grams for boys of the same age group.

Growing children require, in proportion to their weight, a considerably greater protein allowance than do adults. Up to 1 year about 16 per cent of the total Calories of an artificial diet should be furnished by protein (4 grams per kilogram of body weight).² The protein requirement falls gradually until the sixth year when it amounts to about 13 per cent (2.6 grams per kilogram) of the total Calorie requirement. This value is maintained to the end of the period of growth. Children also require a higher proportion of proteins of high biological value (p. 558) than do adults. In young infants high grade proteins should constitute about 100 per cent of the protein allowance (as in milk); at 1 year over 90 per cent, and up to 5 years over 60 per cent. From the latter age to adolescence the proportion should not be far from 50 per cent, and in adult life at least 35 per cent.

Persons undertaking heavy work, undergoing muscular training, or convalescing from wasting diseases also require a more liberal protein allowance. In rigorous climates, protein food, on account of its specific dynamic action, is in higher demand than in warmer localities.

The indispensability of fat

Since body fat can be derived from carbohydrate food it might be thought that dietary fat could be dispensed with. On the contrary, fats quite apart from the fact that they furnish fat-soluble vitamins, are essential elements in nutrition.

Fatty foods contain, besides neutral fats, and fat-soluble vitamins, certain fatty acids which are essential for health and which cannot apparently be synthesized in the body. Rats placed upon a

² In mother's milk the protein calories amount only to 11 per cent of the total. The protein is, however, of higher quality than that of cow's milk.

low fat diet, but containing all the known vitamins, after a time cease to grow but growth is resumed when the essential fatty acids, even in small amounts, are added to the diet. Saturated fatty acids (e.g. oleic) or the animal's own body fat formed from carbohydrate have no protective action. Other effects on rats resulting from a deficiency of the essential fatty acids are, scaliness of the skin, caudal necrosis, emaciation, kidney lesions and early death. The group of *unsaturated fatty acids* which are essential for normal growth and nutrition includes *linoleic* (with 2 double bonds), *linolenic* (3 double bonds) and *arachidonic* (4 double bonds). Actually, only one of these fatty acids is essential, for, as with certain amino-acids, they can replace one another in the diet to a greater or less extent. In fat-deficient animals, the blood lipids have an abnormally low iodine number. In hogs on a low fat diet the linoleic acid content of the lard may be only 1.2 per cent as against a normal of 7 per cent. Puppies upon a diet low in fat develop a scaly or eczematous condition of the skin that is readily cured by feeding lard or other fats. The serum lipids show an iodine number about 25 per cent below normal. It is thought that certain eczematous conditions in the human subject are due to fatty acid deficiency. These subjects show a low content of unsaturated fatty acids in the blood lipids, and babies kept for several months upon a diet very low in fat developed a generalized eczema which was corrected when the fat of the diet was restored. During the period of low fat feeding the iodine number of the serum lipids of these infants was depressed. (See Burr and associates.)

On account of their high energy value fatty foods are demanded in relatively large amounts by men performing very heavy work, especially in cold climates. A pound of beef fat, which contains little water, yields about 4000 calories. The caloric value of an equal amount of white bread, which contains over 40 per cent of water, is only about one-quarter of this. Fat pork, beans and peas (vegetables relatively rich in fat) are prominent items in the diet of Canadian lumbermen and construction workers. The daily energy expenditure of some of the former workers may run to 8000 calories. Another advantage of fat is its superior "staying power." Its digestion and absorption are extended over a much longer period than those of carbohydrates. Hunger, "emptiness" and fatigue are experienced much sooner upon a diet high in carbohydrate than upon one containing a

liberal allowance of fat. The actual efficiency of fat as a fuel for muscular work as shown by Krogh and Lindhard (p. 621) and by Murlin and Marsh is only from 10 to 12 per cent less than that of carbohydrate.

Children, especially those under the age of 1 year, require a larger proportion of fat in the diet than do adults; Holt and Fales place the daily requirement at about 4 grams per kilogram up to the age of 1 year (from 35 to 40 per cent of the total calories) with a gradual reduction to about 3 grams per kilogram at 6 years. According to these

TABLE 67
Ash content of the edible portion of some common foods
(Modified from Lusk)

	IN 100 GRAMS FRESH SUBSTANCE						
	Iron	Calcium	Magnesium	Sodium	Potassium	Phosphorus	Chlorin
	mg.	mg.	mg.	mg.	mg.	mg.	mg.
Beefsteak, lean...	3.8	8	24	67	35	22	50
Liver (beef).....	8.0	11.0
Eggs.....	3.0	67	9	15	14	16	100
Milk, whole.....	0.2	120	11	51	142	94	120
Cornmeal.....	1.1
Oatmeal.....	3.7	93	127	81	380	380	35
Rice, polished...	0.7	8	27	21	68	89	50
Wheat flour.....	1.5	26	30	69	146	86	76
Wheat, entire grain.....	5.2	44	170	106	515	469	88
Beans, lima, dried	7.2	71	187	245	1743	336	25
Beans, string, fresh.....	1.6
Cabbage.....	0.9	49	14	20	243	27	13
Corn, sweet.....	0.8
Peas, dried.....	5.6	100	145	118	880	397	40
Potatoes.....	1.2	11	22	19	440	61	30
Spinach.....	3.8
Turnips.....	0.6	64	169	59	332	51	40
Apples.....	0.3	10	8	15	125	13	4
Raisins.....	3.6	57	9	141	830	126	70

observers, a liberal allowance of fat also favors the absorption of calcium.

Mineral constituents (see also pp. 58, 677 and 709)

Sherman gives the following as the daily requirements of calcium, phosphorus and iron for the average adult (70 kgm. in weight).

Calcium	0.8 gram
Phosphorus.....	1.5 gram
Iron	15-20 mg.

TABLE 67A
Recommended dietary allowances*
(Food and Nutrition Board, National Research Council)

	CALORIES	PROTEIN GRAMS	CALCIUM GRAMS	IRON	VITAMIN A†	THIAMIN (B ₁)	RIBO- FLAVIN	NIACIN (NICO- TINIC ACID)	ASCOR- BIC ACID	VITAMIN D
				mg.	I.U.	mg.†	mg.	mg.	mg.†	I.U.
Man (70 Kg.)										
Sedentary.....	2500	—	—	—	—	1.5	2.2	15	—	—
Moderately active...	3000	70	0.8	12	5000	1.8	2.7	18	75	**
Very active.....	4500	—	—	—	—	2.3	3.3	23	—	—
Woman (56 Kg.)										
Sedentary.....	2100	—	—	—	—	1.2	1.8	12	—	—
Moderately active...	2500	60	0.8	12	5000	1.5	2.2	15	70	**
Very active.....	3000	—	—	—	—	1.8	2.7	18	—	—
Pregnancy (latter half).....	2500	85	1.5	15	6000	1.8	2.5	18	100	400 to 800
Lactation.....	3000	100	2.0	15	8000	2.3	3.0	23	150	400 to 800
Children up to 12 years:										
Under 1 year§.....	100/kg.	3 to 4/kg.	1.0	6	1500	0.4	0.6	4	30	400 to 800
1-3 years¶.....	1200	40	1.0	7	2000	0.6	0.9	6	35	**
4-6 years.....	1600	50	1.0	8	2500	0.8	1.2	8	50	—
7-9 years.....	2000	60	1.0	10	3500	1.0	1.5	10	60	—
10-12 years.....	2500	70	1.2	12	4500	1.2	1.8	12	75	—
Children over 12 years:										
Girls, 13-15 years...	2800	80	1.3	15	5000	1.4	2.0	14	80	**
16-20 years...	2400	75	1.0	15	5000	1.2	1.8	12	80	—
Boys, 13-15 years....	3200	85	1.4	15	5000	1.6	2.4	16	90	**
16-20 years....	3800	100	1.4	15	6000	2.0	3.0	20	100	—

* Tentative goal toward which to aim in planning practical dietaries; can be met by a good diet of natural food. Such a diet will also provide other minerals and vitamins, the requirements for which are less well known.

- † 1 mg. thiamin equals 333 I.U.; 1 mg. ascorbic acid equals 20 I.U.
- ‡ Requirements may be less if provided as vitamin A; greater if provided chiefly as the pro-vitamin carotene.
- § Needs of infants increase from month to month. The amounts given are for approximately 6-8 months. The amounts of protein and calcium needed are less if derived from human milk.
- ¶ Allowances are based on needs for the middle year in each group (as 2, 5, 8, etc.) and for moderate activity.
- ** Vitamin D is undoubtedly necessary for older children and adults. When not available from sunshine, it should be provided probably up to the minimum amounts recommended for infants.

Further Recommendations, Adopted 1942:

The requirement for *iodine* is small; probably about 0.002 to 0.004 milligram a day for each kilogram of bodyweight. This amounts to about 0.15 to 0.30 milligram daily for the adult. This need is easily met by the regular use of iodized salt; its use is especially important in adolescence and pregnancy.

The requirement for *copper* for adults is in the neighborhood of 1.0 to 2.0 milligrams a day. Infants and children require approximately 0.05 per kilogram of bodyweight. The requirement for copper is approximately one-tenth of that for iron.

The requirement of *vitamin K* is usually satisfied by any good diet. Special consideration needs to be given to newborn infants. Physicians commonly give vitamin K either to the mother before delivery or to the infant immediately after birth.

In childhood and in pregnancy (especially in the later months) and in lactation the calcium requirement is higher than that given above. For children of from 3 to 20 years the minimum is placed at 1.0 to 1.4 gram per day. In the later months of pregnancy when from 20 to 30 grams of the

mineral are being deposited in the fetus, the daily allowance should be at least 1.5 gram; 2 grams should be the daily allowance during lactation. The best source of calcium for the growing child is milk, which contains about 1.3 grams per quart. Cereals also are rich in calcium though much of it is not available; meat contains insignificant amounts of this element (see table 67). Milk and other dairy products are good sources of available phosphorus. Though cereals and many vegetables contain this element in much larger amounts the greater proportion of it is not utilized (p. 711). Egg yolk, meat, liver and kidney, certain vegetables, fruits and nuts are the main sources of iron. Milk is very poor in this element.

The daily requirement of iron for children is about 0.5 milligram per kilogram of body weight; milk-fed infants therefore tend to develop anemia (p. 63) after the fourth month or so unless given iron in inorganic form.

Protein foods are rich in phosphorus, and so long as the diet contains a sufficient quantity of protein and is well balanced in other respects, no special

attention need be given to the phosphorus content of the diet. Phosphorus deficiency is seen in farm animals fed upon the produce of soils deficient in this mineral.

The basic elements, sodium, potassium and magnesium, are derived chiefly from cereals, fruits and vegetables. Sodium chloride is also taken in the form of cooking and table salt. The average daily intake is from 10 to 12 grams. Many preparations of table salt are also sources of iodine, since it has become the custom of the manufacturer to add minute quantities of this element to his product. The daily iodine requirement for adults is from 0.15 to 0.30 milligram.

The dietary allowances recommended by the food and nutrition board of the National Research Council, Washington, are given in table 67a. Some of the allowances, especially those for thiamin and ascorbic acid, may be unnecessarily high. Dietary surveys indicate that good nutrition is maintained upon intakes of these vitamins with values less than half those given in the table (see Riggs and associates and Ferguson, Leeson and McHenry).

SECTION VII. THE DUCTLESS GLANDS OR ENDOCRINES

CHAPTER LVIII

INTRODUCTION. THE THYROID GLAND

DEFINITIONS. NATURE OF HORMONES. METHODS OF INVESTIGATING ENDOCRINE FUNCTION

(The products of the ductless glands—thyroids, adrenals, pituitary, etc.,—belong to a class of physiologically active chemical substances known as *internal secretions or hormones*.) The latter term was first used by Bayliss and Starling in the report of their discovery of secretin (p. 451), it is derived from a Greek word meaning to excite. Though nearly all the actions of the secretions of the ductless glands are excitatory in character a few internal secretions (e.g., enterogastrone, p. 436) are inhibitory. The term *chalone* has been suggested for the latter by Schafer but is not often used. (A hormone may be defined as a chemical substance which, having been formed in one part of the body, is carried in the blood stream to another organ or tissue and influences its activity.) With the exception of the secretions of the thyroid, gonads and adrenal cortex, the various hormone preparations which so far have been obtained by extraction and employed in medicine, are almost or quite inert when administered orally. Even though the sex hormones and the principles of the adrenal cortex are effective by oral administration, the dose when given in this way must be much larger than if given parenterally in order to produce the same response. Adrenaline, insulin and the principles of the parathyroids and pituitary, in order to be effective, must be given by injection. Most of the ductless glands are present in all orders of vertebrates and an extract obtained from the gland of one order exerts, as a rule, its specific effect when administered to a member of another order, e.g., the hormone of the sheep's thyroid influences the growth and development of frog larvae (tadpoles). (See also p. 671.)

Apart from small amounts which may be held in the endocrine organs themselves, hormones are not stored in the body. Therefore, in cases of endocrine deficiency, repeated small doses rather than large doses at infrequent intervals are required to correct the deficiency. A hormone does not stimulate the gland which secretes it. Thyroid extract, for example, does not stimulate the

thyroid; and the ovarian hormones do not stimulate the ovary directly.

Three main methods are available for the study of an endocrine function. *First*, an extract of the gland tissue may be prepared which may then be injected into animals and a study made of its effects. *Secondly*, a particular gland may be removed from an animal and the subsequent life history of the animal watched, careful notice being taken of its subsequent development, growth, or any unusual symptom. Or, *thirdly*, studies may be made upon human subjects in whom one or other gland is known to be deficient or overactive.

A few words may be written here concerning the general chemical nature of the active principles of the endocrines. The hormones of the sex glands and adrenal cortex are steroids and closely allied in chemical structure, while the active principles of the pituitary, thyroid and parathyroids are proteins.

THE THYROID

Development, histology, blood and nerve supply

Very early in its evolutionary history the thyroid had a digestive function, a function lost long since but which its ontogeny recalls. The gland is developed from a single median outgrowth of hypoblast derived from the ventral wall of the primitive pharynx at the level of the 1st visceral cleft. This extends downwards. Its lower end bifurcates and enlarges to form the isthmus and lateral lobes of the thyroid. Its upper end gives rise to the foramen cecum of the tongue. The intervening portion—the *thyro-glossal duct*—normally disappears but sometimes persists and may give origin to accessory thyroids or to the so-called thyro-glossal cysts.

The *thyroid tissue* is composed of cuboidal epithelial cells arranged in a single layer around spaces roughly circular in shape and fairly uniform in size. These spaces, variously known as *vesicles*, *acini* or *alveoli*, contain a homogeneous gelatinous material—the *colloid substance*—which is the stored secretion of the gland. Connective tissue fibers support the alveolar walls and form septa which divide the gland into smaller masses. The cells lining the alveoli contain numerous mitochondria and a well defined Golgi apparatus. When the gland becomes active the Golgi apparatus hyper-

trophies and droplets of colloid appear in its proximity. The maximal normal weight of the human thyroid is, according to Marine, from 20 to 35 grams or around 0.4 gram per kilogram of body weight. The thyroid tissue of the early fetus consists of masses of epithelial cells showing little or no arrangement into acini. The latter appear about the 4th month but are small and contain little colloid.

The *blood supply* comes from the superior and inferior thyroid arteries, chiefly the former. The blood flow is profuse, the blood passing with little resistance from the arterial to the venous side through a wide capillary bed. The flow amounts to from 3.5 to 6 cc. per gram of tissue per minute, or about 5 liters per hour for the whole gland. The gland is richly supplied with *lymphatics* which drain lymph spaces surrounding the vesicles.

The *nerve supply* of the thyroid is derived from the vagus and the sympathetic. The sympathetic fibers leave the spinal cord between the 2nd and 5th thoracic segments and pass to cell stations in the superior and middle cervical ganglia, whence they are relayed to the gland through the superior laryngeal nerves and along the blood vessels. It is probable that the thyroid nerves are purely vasomotor in function and influence the activity of the gland indirectly, namely, by altering its blood supply. Control of thyroid activity is exerted mainly, if not exclusively, by the thyrotropic hormone of the pituitary (p. 725).

AN OUTLINE OF THYROID FUNCTION

Some of the first experiments upon the thyroid were performed in 1856 by Schiff who found that in dogs death followed its removal; from the symptoms preceding death it is now apparent that this was due to removal of the parathyroids (p. 700). As in the case of some other ductless glands, clinical observations gave the first hint concerning the functions of the thyroid. Hilton Fagg in 1871 reported a case of *cretinism* (p. 673) and ascribed it to absence or atrophy of the thyroid. Three years later Gull described the condition which today is known as *myxedema* or *Gull's disease*, but called it the *cretinoid state in adult life*. Horsley some years later removed the gland from monkeys and produced conditions resembling human cretinism and myxedema. Later experiments upon other species have established the fact that the thyroid secretion is absolutely necessary for the normal growth and development of young animals, and for maintaining the normal level of metabolism of animals of all ages. Magnus-Levy in 1895 demonstrated that thyroid deficiency was associated with a greatly reduced metabolism and that treatment with desiccated thyroid restored the metabolic rate to the normal level or above. Com-

plete thyroidectomy reduces the basal metabolic rate by from 40 to 45 per cent in about 8 weeks after the operation. Thyroidectomy in lambs, young rabbits, goats or calves has been shown to cause retarded skeletal growth and arrested sexual development (fig. 260). Apathy, lack of vigor, thickening of the skin, and a striking reduction in basal metabolism result in both young and full-grown animals. In young cattle increase in bulk but not in height is a notable feature; the animals appearing short-legged and of a broad, stocky build. Other effects of thyroid removal in the young are; delay in the ossification of the epiphyses of the long bones; poor growth of hair; failure in thymic involution; and subnormal intelligence.



FIG. 260. Triplet kids. Center animal normal; right- and left-hand animals thyroidectomized at 20 days old. Photograph taken 13 weeks after operation. (After Sutherland Simpson.)

The administration of thyroid extract to young animals shortly after thyroidectomy prevents these otherwise inevitable results. In full-grown animals the effects of thyroid removal can be corrected by thyroid administration at any time after operation.

The effects produced upon lower orders by thyroid removal and by thyroid feeding are even more striking. Gudernatch removed the thyroids from tadpoles, keeping a number of young animals of the same hatching as controls. The thyroidectomized larvae grew somewhat larger in size but did not metamorphose, though the controls developed into frogs within the usual time (fig. 261). Metamorphosis of the thyroidless creatures could be induced to proceed at the normal rate by thy-

roid feeding.¹ Also, the time required for the normal larvae to metamorphose completely could be shortened (from 104 to 20 days) by feeding thyroid tissue. Swingle has shown that inorganic iodine alone will produce similar effects. The effect of the thyroid hormone upon the axolotl is extraordinary. This animal is allied to the frog, but is purely aquatic in its habits. It has, in its adult form, a finned tail, gills and four short limbs, resembling somewhat an enormous tadpole which has undergone partial metamorphosis. Thyroid feeding causes the axolotl to lose its fin and gills, develop air breathing organs and forsake the aquatic life for which nature had designed it. See also pages 683 and 726.



FIG. 261. The effect of the removal of the thyroids upon the development of tadpoles A, thyroidless tadpoles. B, normal frogs of the same age as A. (After Allen, redrawn.)

In growing birds (chicks) and mammals, a stimulating effect of the thyroid hormone on growth has been demonstrated. Acceleration of growth has also been observed in a twin child suffering from hyperthyroidism.

THE RELATION OF THE THYROID TO THE PITUITARY, ADRENALS AND GONADS

The thyroid-pituitary relationship is considered in Chapter LXI. A relationship between the thyroid and adrenals is indicated by the following observations. (a) Subjects of hyperthyroidism show increased susceptibility to adrenaline administration (Goetsch test). In animals, the

¹ This effect has been made use of to assay the potency of thyroid preparations or to determine the activity of a particular thyroid gland (Gudernatch test).

threshold dose of adrenaline for cardiac acceleration is reduced by a previous administration of thyroid hormone. (b) Thyroxine (p. 681) administration to normal dogs causes hyperglycemia; this does not occur if the adrenal veins have been tied before injection of the thyroid hormone. (c) Marine and Baumann found that injury to the adrenal cortex caused an increase of 60 per cent in heat production. No change in metabolism occurred, however, if the metabolic rate had first been reduced as a result of thyroidectomy. Marine suggests that the adrenal cortex normally exerts, through the pituitary, some inhibitory control over thyroid function.

The following observations suggest an interrelationship between the thyroid and gonads. (a) Thyroid enlargement is frequently observed at puberty and during menstruation or pregnancy. (b) Castration in the dog or rabbit usually leads to a slow reduction in the size of the thyroid and a depression of the metabolic rate (Marine). (c) The continued injection of estrogenic substances into rats or guinea pigs causes thyroid enlargement followed after a few days by involution of the gland. (d) Thyroid feeding is said to inhibit estrus. These thyroid-gonadal relationships are probably brought about through the pituitary.

GOITER

Goiter is a generic term which may be applied to almost any non-inflammatory and non-malignant enlargement of the thyroid gland. The following is a short classification:

- A. *Simple goiters. These are unaccompanied by constitutional features. They are subdivided upon a histological basis into three groups:*
 - (1) Colloid (diffuse)
 - (2) Parenchymatous (diffuse)
 - (3) Adenomatous (nodular)
- B. *Goiters associated with a deficiency of the thyroid hormone (hypothyroidism)*
 - (1) Cretinism
 - (2) Myxedema
- C. *Goiters associated with an excess of the thyroid hormone (hyperthyroidism)*
 - (1) Exophthalmic goiter
 - (2) Toxic adenoma

Diffuse colloid goiter

The alveoli are large, distended with colloid and lined by low cuboidal or flattened epithelial cells. There is no hypertrophy or hyperplasia of the latter (fig. 262 and lower photograph, fig. 266). The iodine content per gram of gland tissue is low but

as a rule the total quantity in the enlarged gland is not far from normal. Colloid goiter may become converted into, or result from, the following type (see also pp. 677-680).

Diffuse parenchymatous goiter

Hypertrophy and multiplication of the cells lining the alveoli, with great reduction in the amount of colloid material are characteristic features of this type. The alveolar cavities are of various sizes and shapes and often almost obliterated by infoldings of their walls. The epithelial cells are high columnar in type. The iodine content of the gland is low, usually much less than 0.1 per cent of its dried substance. Exhaustion of the

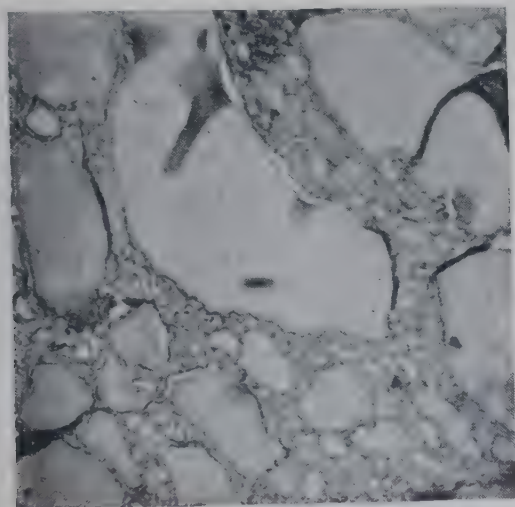


FIG. 262. Photomicrograph of a human simple colloid goiter.

gland and atrophy of its secretory elements with an increase in fibrous tissue may result, or, as mentioned above, the goiter may change to the colloid type, especially after iodine administration (fig. 266). Partial thyroidectomy in animals, as first shown by Halsted, results in regeneration of the thyroid remnant to produce the foregoing histological picture of diffuse parenchymatous hypertrophy. This observer also showed that removal of the thyroid from pregnant bitches led to parenchymatous goiter in the puppies.

Adenomatous goiter

As a result of the formation of isolated tumor-like masses of thyroid tissue (adenomata) the glandular enlargement is asymmetrical or nodular. The minute structure of the adenoma may resemble a section of colloid or of parenchymatous goiter, or it may undergo cystic changes. Again, the alveoli may be unusually small, contain little colloid and resemble fetal thyroid tissue (fetal adenoma):

The iodine content of the nodule may be normal or high while that of the rest of the gland, which may also show diffuse colloid or parenchymatous changes, is usually low.

The simple enlargement of the thyroid which sometimes occurs at puberty or during pregnancy may be either of the colloid or parenchymatous type. A certain degree of thyroid enlargement at



FIG. 263. Upper photograph (left), cretinism in an infant; (right), same child after treatment with thyroid extract. (After J. Huxley.) Lower photograph, a cretin aged 10 years. (From McCarrison after Thomson.)

these times is physiological. The enlargements seen in goiter districts (endemic goiter) or occurring sporadically may show the features of any of the three types. Either of the first two forms may end in exhaustion atrophy (p. 677).

HYPOTHYROID STATES

Cretinism

A cretin is a type of dwarf for which deficiency or absence of the thyroid secretion in infancy or early childhood is directly responsible (fig. 263).

Among the typical features of the condition are: (1) retarded and abnormal skeletal growth; (2) arrested sexual development; (3) mental deficiency varying in degree but often amounting to complete idiocy; deaf mutism is common; (4) the facial features are coarse and appear bloated, the skin is dry, thick, pasty and often deeply wrinkled; the nose is broad and its bridge depressed; the tongue is enlarged and appears between the thickened and usually parted lips; (5) the supraclavicular fossae are filled with pads of fat; (6) closure of the anterior fontanelle which normally occurs before the 20th month is postponed for several years; the epiphyses of the long bones fail to ossify at the usual time; (7) the basal metabolic rate is depressed by from 20 to 40 per cent below the normal.



FIG. 264. Left, myxedema. Right, same subject after three months treatment with thyroid extract. (After Murray.)

Endemic cretinism is much less common today. In the past it was seen most frequently in districts where goiter was prevalent—in the valleys of the Alps, Pyrenees, Himalayas, etc.—and was usually the result of atrophy and degeneration of the secretory epithelium of a goitrous gland. Some of the worst cases of cretinism appear, however, in infants, either in these districts or elsewhere, who are not goitrous. The condition is then due to: (a) prenatal or early postnatal atrophy of the thyroid, (b) to its congenital absence, or (c) to its destruction by some inflammatory condition. A large percentage of the goiterless cretins in a goiter district are the result of hypothyroidism in one or both of the parents.

Though the majority of cretins are apathetic and sluggish, some are highly excitable—the *nervous cretinism of McCarrison*.

Myxedema (Gull's disease)

Myxedema is the result of thyroid deficiency in adults or older children and corresponds to the cretinism of infants and younger children. It follows atrophy or destruction of the thyroid from whatever cause, or may result from an operation in which too much of the gland has been removed (*operative myxedema* or *cachexia strumipriva*). The chief characteristics are (a) low metabolic rate (-20 to -40); (b) a thick puffy appearance of the skin; the hair is dry, brittle and sparse; the facial features sometimes give the subject a mongoloid look (fig. 264); (c) apathy, lethargy, slow cerebration, though general intelligence is retained; (d) increased body fat and hypercholesterolemia;

(e) greater susceptibility to cold and (f) cardiac dilatation and low voltage electrocardiograms. The edema-like appearance of the skin was thought by Ord, who suggested the term myxedema, to be due to the accumulation of mucin in the subcutaneous tissues. The thickening of the skin is not due to a true edema, nor is it the result of the accumulation of mucin but, according to Boothby, to the deposit of a semi-fluid albuminous substance containing over 13 per cent of protein, or about the concentration of protein in white of egg. This deposit is looked upon by Boothby and his associates as representing an increase in the normal quantity of stored or deposit protein (p. 546).

A non-myxedematous condition associated with a 20 per cent reduction of the basal metabolic rate, undue susceptibility to fatigue, increased sensitivity to cold and sometimes nutritive abnormali-

ties of the skin, hair and nails is recognized. It is ascribed to a relatively mild grade of hypothyroidism.

HYPERTHYROID STATES

Exophthalmic goiter (Graves' or Basedow's disease)

In Graves' disease there is nothing in the histological appearance of the thyroid to distinguish it, with certainty, from a simple goiter. The gland usually shows a picture typical of parenchymatous goiter, i.e., hypertrophy and hyperplasia (p. 673); its iodine content is low. The blood iodine is elevated. After iodine administration the gland tends to assume the histological appearance of colloid goiter (fig. 266). The blood supply of the gland is greatly increased, the rush of blood through the superior thyroid arteries often producing a loud bruit or a distinct thrill. In addition to the thyroid enlargement the chief features of the fully developed condition are:

(a) Accelerated pulse (100 to 160 per min.) and increased circulation rate (50 per cent or more above normal); cardiac dilatation and hypertrophy; myocardial failure; auricular fibrillation in 20 per cent of cases; flushing of the skin; normal or low diastolic pressure with high systolic pressure (i.e., high pulse pressure).

(b) Nervous excitability.

(c) Muscular weakness and a fine involuntary tremor.

(d) Protrusion of the eyeballs (exophthalmos) and other ocular signs, e.g., widening of the palpebral fissure (Stellwag), as a result of retraction of the upper lid; and infrequent winking; lack of convergence of eyes (Moebius); slow jerky movement of the upper lid or its failure to follow the eye when looking down (von Graefe) (fig. 265).

(e) Metabolic rate increased to varying degrees up to 80 per cent above normal. As a result of the increased activity of the heat-dissipating mechanisms the skin is hot and moist. Increased tolerance to cold and lowered tolerance to a high environmental temperature.

(f) Dissipation of the fat stores; wasting.

(g) Nitrogen and calcium excretion are increased (rarefaction of the skeleton may be demonstrated by X-rays in many cases).

(h) Disturbance of carbohydrate metabolism is common, as evidenced by hyperglycemia, glycosuria and reduced sugar tolerance. Hepatic glycogen stores are reduced.

(i) The thymus is enlarged in 80 per cent of cases.

(j) Subjects of hyperthyroidism are especially susceptible to oxygen deficiency. Work is performed less economically and dyspnea occurs upon exertion (p. 356).

With regard to some of the foregoing features. The tachycardia is not dependent upon nervous connections but appears to be due to a direct and persistent effect of the hormone upon the cardiac musculature. The excised heart of an animal given thyroxine (p. 681) in excess, beats at the increased rate when perfused, or transplanted to the body of another animal. Also, fragments of heart muscle of a two-day-old chick embryo pulsate at a more rapid rate when thyroxine is added to the nutrient fluid. The high pulse pressure seen in hyperthyroidism is due to the general vasodilatation combined with an increased stroke volume. The increased circulation rate is chiefly



FIG. 265. Typical case of exophthalmic goiter showing characteristic facies. (After Crile.)

the result of the higher metabolic rate. The cause of the cardiac hypertrophy and ultimate failure is not altogether clear. In some instances it is probably simply the result of the increased work (greater circulation rate) thrown upon a myocardium already affected by some other disease (hypertension, valvular lesions, etc.). It is also probable that the cardiac condition is dependent upon a specific effect of the thyroid hormone upon the heart muscle. According to Hurxthal the latter is a more potent factor than the increased mechanical work. This observer believes, however, that neither of these factors will induce hypertrophy and failure of a normal heart but that myocardial damage must have pre-existed (see also p. 220). Exophthalmos has been attributed to the contraction of Mueller's muscle situated at the back of the orbit or of the smooth muscle

situated in the fascia bulbi. The contraction of Mueller's muscle was believed, by compressing the orbital contents, to push the eyeball forward. This view was supported by the fact that experimental stimulation or section of the sympathetic in the neck (from which the innervation of this muscle and of the smooth muscle of the fascia bulbi is derived) causes, respectively, protrusion or recession of the eyeball. But, whereas in animals Mueller's muscle is well developed, in man it is a mere vestige and, according to Whitnall, is not concerned in the production of the exophthalmos. Smooth muscle in the fascia bulbi of man, is too small in amount to exert a force which could possibly protrude the eyeball against the restraining action of the ocular muscles (recti). According to Whitnall, the exophthalmos is primarily due to dilatation of the orbital venules and the transudation of fluid into the post-ocular tissues. The absence of lymphatics from this region encourages the accumulation of the transudate; subsequently, organization with hypertrophy of the orbital tissue occurs. Smeltser produced exophthalmos in guinea-pigs by means of daily injections of the thyrotropic hormone of the pituitary and then examined the orbital contents histologically. He found changes closely resembling those observed in the exophthalmos of Graves' disease, namely, edematous and lymphoid infiltrations of the orbital tissues which were increased considerably in bulk. He states that these effects of the thyrotropic hormone can be prevented to some extent by excision of the cervical sympathetic ganglion (which one is not stated). (See also pp. 677, 725.) There appears to be no correlation between exophthalmos and the level of the basal metabolism or any of the other manifestations of hyperthyroidism; indeed, exophthalmos may persist and even progress after thyroidectomy, though the basal metabolism has fallen to normal or below, and other signs of hypothyroidism have supervened. The signs of exophthalmic goiter referable to the eyelids (Stellwag's and von Graefe's) are possibly due to stimulation of the smooth-muscle component of the levator palpebrae superioris (p. 1016) which is innervated by the sympathetic.

Thyroid crises. During the course of exophthalmic goiter intense exacerbation of the symptoms may occur, accompanied by nausea, vomiting, diarrhea, dehydration, high temperature, a great increase in heart rate, erythema, extreme nervousness, thrashing about in bed, muscular weakness, and sometimes delirium or coma. Such a crisis

may occur after operation, and death result from exhaustion or cardiac failure.

Toxic adenoma

A simple adenomatous goiter (p. 673) may undergo increased functional activity and produce the features of pure hyperthyroidism, i.e., those produced by the administration of thyroid extract in excessive amounts, or those described under exophthalmic goiter *minus* the exophthalmos and crises. A simple adenomatous goiter does not give rise to hyperthyroidism until the lapse, on the average, of fifteen years (Plummer). Toxic adenoma occurs at a later age than exophthalmic goiter, which is usually neither preceded by a goitrous condition nor is more prevalent in goitrous districts.² It is said that about 20 per cent of adenomatous goiters eventually become toxic. A toxic adenoma possesses no histological features which distinguish it with certainty from the simple variety.

DISCUSSION OF THE FOREGOING HYPERTHYROID STATES

Many authorities do not draw any physiological or other essential distinction between the two types of hyperthyroidism believing that there is but one disease which differs only in its clinical manifestations. Others find it difficult to believe that certain features of exophthalmic goiter (e.g., exophthalmos, more rapid development, greater nervous excitability, crises and a more favorable reaction to iodine administration) do not indicate a fundamental difference between it and toxic adenoma. Two theories have been advanced in explanation. Plummer, who first separated clinical hyperthyroidism into these two types, believed that in toxic adenoma hyperfunction of the gland alone was evident, whereas in exophthalmic goiter there was dysfunction as well; he suggested that in the latter disease the gland formed not only an excess of the normal hormone, but also one which was abnormal as a result of incomplete saturation of its molecule with iodine (*two-secretion hypothesis*). According to this theory administration of iodine was beneficial presumably because it permitted the formation of a normal secretion. Marine contends, on the other hand, that exophthalmic goiter is not due primarily to thyroid disease, but to a disturbance of some other

² According to Pemberton the last statement applies to Europe, not to America in which the incidence of exophthalmic goiter is higher in goitrous districts.

docrine. The sympatho-adrenal system has been suggested in this connection. Recent work points to involvement of the anterior lobe of the pituitary (p. 680) or the pituitary-hypothalamic mechanism. The underlying disorder whatever it may be, causes stimulation of the gland which in turn is responsible for the raised metabolic rate and other manifestations attributable to the excessive secretion of its hormone. The other features, e.g., the exophthalmos and crises are ascribed to the primary disorder itself. The conception of an extra-thyroid factor is supported by the following observations. (a) The exophthalmic type of thyrotoxicosis is frequently sudden in onset, rapid in development and may appear though there has been no previous thyroid disease. (b) Exophthalmos is rarely, if ever, produced by the administration of thyroid hormone to animals, nor does it occur, except very occasionally, in adenomatous goiter, though signs of hyperthyroidism are clearly evident. Marine and Rosen, on the other hand, have produced exophthalmos in *thyroidectomized* guinea pigs by means of injections of anterior pituitary extracts (see also pp. 681 and 725); and clinically, exophthalmos and nervous manifestations sometimes persist though the thyroid hyperplasia is reduced and the basal metabolic rate returns to normal; the thyrotropic hormone then appears in excessive amounts in the urine. (c) An extract of the gland from subjects of exophthalmic goiter is no more toxic than that of a normal gland, often much less so, when administered to animals or to another victim of the disease. (d) The toxicity of such an extract is proportional to its iodine content. This is the opposite to what one should expect if an iodine-deficient product were responsible for some of the features of the disease. Furthermore, evidence from the chemical side is against the view of a compound poor in iodine being responsible for the toxic symptoms. Diiodothyronine, for example, which is thyroxine less two atoms of iodine, has the same but has an activity only about 4 per cent of the activity of thyroxine itself (p. 681). Thyronine which contains no iodine is inactive. (e) The features of the thyroid crises suggest a profound disturbance of involuntary nervous centers; furthermore, some of the most severe crises are postoperative, i.e., after a large part of the gland has been removed.

THE RÔLE PLAYED BY IODINE IN THYROID FUNCTION

Iodine is an essential element of the thyroid hormone and its administration exerts a profound

effect upon the thyroid tissue. Simple goiter is due to iodine deficiency. This may be (a) an *absolute deficiency* in water and food, (b) a *relative deficiency*, the iodine of the food being sufficient for the elaboration of the amount of hormone required under the ordinary circumstances of life but insufficient under more exacting conditions, e.g., puberty, pregnancy, excessive protein of the diet, etc. (c) It is also possible that certain microorganisms in the intestinal tract may reduce the quantity of iodine absorbed from the food; this would explain McCarrison's observations upon the relationship between the incidence of goiter in India and infected drinking water. It is more likely, however, that infected water, if it does sometimes play a part in the production of goiter, acts in some other way than by merely interfering with the absorption of iodine.

The quantity of iodine in the normal thyroid is about 2 mg. per gram of dried tissue; the average total store in the gland is from 10 to 15 mg. A content below 1 mg. per gram of dry gland according to Marine, is indicative of definite thyroid abnormality; in severe parenchymatous goiter, either simple or exophthalmic, it may be as low as 0.25 mg. or less per gram. In colloid goiters the general level is higher. Marine considers all goitrous enlargements, including the exophthalmic type, as examples of "a compensatory work hypertrophy," brought about by iodine deficiency. The demands made upon the gland to produce its hormone without an adequate iodine supply results in hypertrophy and hyperplasia, or adenomatous growth, and in some instances, final exhaustion and atrophy. This conception is well supported by the following facts: (a) The degree of hyperplasia of the gland is inversely related to its iodine content. When hyperplasia gives place to exhaustion atrophy, the gland is almost iodine-free. (b) A colloid goiter which is an expression of moderate iodine deficiency passes into the hyperplastic type when the iodine intake is further reduced. (c) The parenchymatous hyperplastic picture is converted to the colloid type upon the administration of iodine (fig. 266). Iodine thus induces the storage of colloid (thyroglobulin). The types of simple goiter are looked upon as stages in a process which is responsive to the iodine supplies, the gland sometimes passing several times through a cycle of hypertrophic, hyperplastic and colloid changes; or the cycle may end in atrophy. The successive stages are represented in the following scheme after Marine.

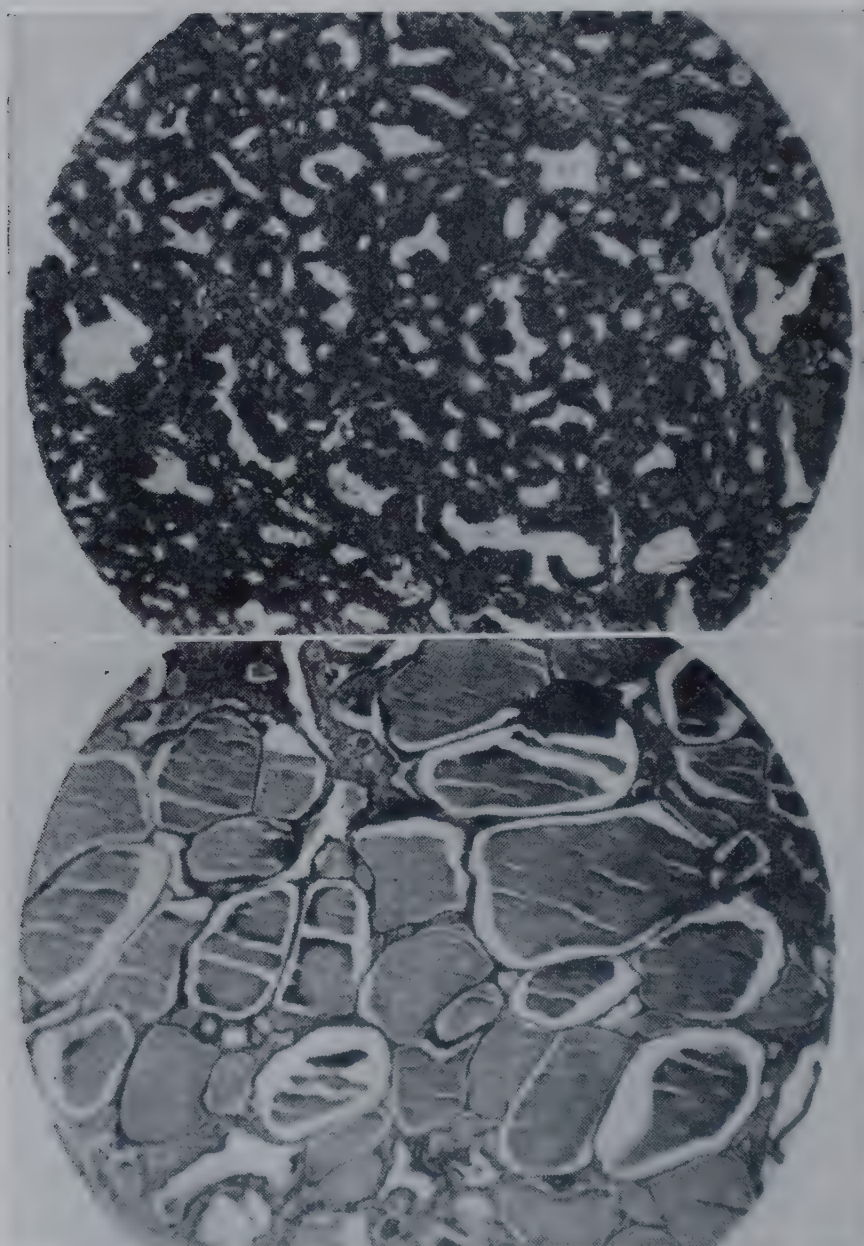
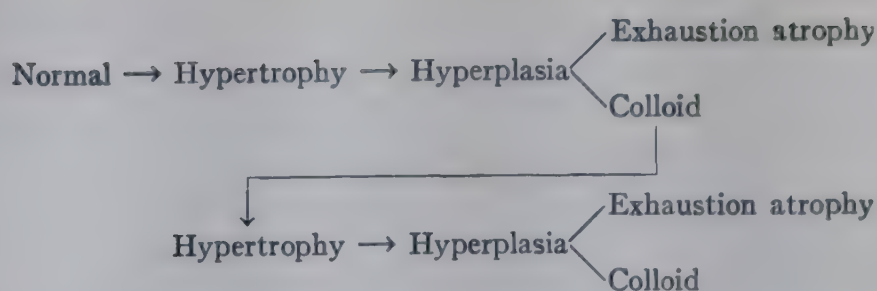


FIG. 266. Upper photograph. Microscopical appearance of the gland in exophthalmic goiter showing hypertrophy and hyperplasia (parenchymatous goiter) before the administration of iodine. Lower photograph, showing appearance after involution had occurred from iodine administration (colloid goiter). (After Rienhoff.)

The thyroid tissue as shown by Marine has a striking affinity for iodine. The gland though constituting only 0.05 per cent or less of the body weight contains about 20 per cent of the body's entire supply of iodine. Marine showed that when the thyroid was perfused with a solution of potassium iodide, relatively large quantities of iodine were taken up by the gland and could not be removed by subsequent washing. This result was not obtained by the perfusion of other organs, e.g., spleen, kidney, etc. The selective action of the intact thyroid for ingested iodine was also demon-

strated. Over 18 per cent of iodine fed to normal animals was recovered from the gland; the fetal gland also stores iodine fed to the mother. According to Salter, the concentration in the blood of the protein bound fraction shows a closer correlation with the symptoms of hyperthyroidism than does the basal metabolic rate.

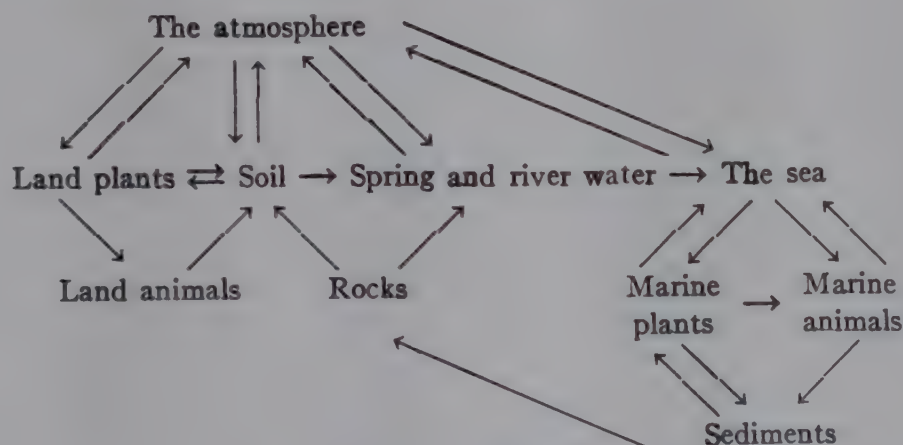
Blood normally contains from 10 to 12 micrograms (0.010 to 0.012 mg.) per cent. In hyperthyroidism it is nearer 30 micrograms per cent and in hypothyroidism between 7 and 9 micrograms. In health from 25 to 75 micrograms of iodine are

excreted daily in the urine. Most of the blood iodine is in organic form, only a small fraction, probably of dietary origin, being inorganic. The organic portion is bound to protein from which it can be extracted. In the extract are a di-iodotyrosine-like and a thyroxine-like fraction. Knowledge of this subject has been advanced in recent years by the use of radioactive iodine. It has been shown by its aid that the hyperplastic gland has a greater avidity for iodine than has a normal gland, absorbing 80 per cent of a dose (2 mgm.) of iodine within 10 minutes after intravenous injection. A later analysis of the thyroid tissue shows that the free iodine concentration has been quickly reduced and the concentration of thyroxine increased.

Elmer has developed an *iodine tolerance test* based upon the especially high affinity of hyperplastic thyroid tissue for iodine. In performing the test as modified

investigations into the relationship between iodine and goiter; he showed that the iodine content of the soil, water and air of goitrous districts was very low. He attributed the thyroid enlargement to this deficiency, and recommended iodine administration as a preventive. Goiter is not seen along the sea-board. The sea contains an inexhaustible supply of iodine which has been leached from the soil and carried to the ocean in streams and rivers. Sea water contains about 0.02 mg. of iodine per liter, fresh water, as a rule, very much less. The further away from the ocean and the more mountainous the country, the lower is the concentration of iodine in food and water and the higher in consequence is the incidence of goiter.

The following schema modified from Lunde shows the distribution and circulation of iodine in nature:



The circulation of iodine in nature

by Perkin and his colleagues 10 cc. of blood are withdrawn and its iodine content determined; 37 mg. of iodine in the form of Lugol's solution are then given by mouth and the blood iodine determined in samples taken at half-hour intervals during the succeeding two and a half hours. The test, it is claimed, gives valuable aid in the diagnosis of borderline cases of thyroid disease. The curves drawn from the data are considerably higher for normal persons and for those with non-toxic adenomatous goiter, reaching a maximum of around 180 micrograms per cent, than for hyperthyroid subjects (max. 40 micrograms per cent).

Iodine in the prevention and treatment of goiter

Burnt seaweed or sponge, both of which are rich in iodine, have been employed in the treatment of goiter from the days of Hippocrates. Following the discovery of the element in the early part of the nineteenth century, its administration for the cure of many ills, but especially of goiter, became the vogue. As a result of its indiscriminate use its real value was soon lost sight of. Chatin from 1850 to 1860 carried out some of the first scientific

To Marine and his associates is due the credit for establishing the value of iodine in the prevention of goiter. They found that iodine or sea food prevented the thyroid enlargement in brook trout hatcheries. Marine and Kimball carried out experiments upon a large number of school children in Akron, Ohio, where goiter was endemic. They showed that of the group of children given iodine (2 grams sodium iodide in 10 daily doses twice a year) those who developed goiter amounted to only a small fraction of the number of goitrous individuals in a control group in which the iodine intake was not increased above that of the general population. The employment of small amounts of iodine in goiter districts such as Switzerland, New Zealand, Derbyshire in England and in parts of the United States and Canada has proved to be a preventive measure of the utmost value. By the use of this prophylactic, animal breeders in goiter districts have almost entirely eradicated the disease from their live-stock. Once goiter has become established iodine administration is of much

less value but, as already mentioned, a hyperplastic parenchymatous goiter may be converted thereby to the less severe colloid type. Iodine in the form of Lugol's solution³ (10 to 40 minims daily) is invaluable in the treatment of exophthalmic goiter; hyperplasia gives place to the picture of colloid goiter (fig. 266), the symptoms abate, there is a pronounced fall in the basal metabolic rate and the danger of a thyroid crisis is reduced, or, if a crisis has commenced, it may be ameliorated or checked. In the Mayo Clinic, the surgical mortality has been lowered from 3.5 to 0.7 per cent and pre-operative deaths from 2.5 to less than 0.5 per cent since iodine treatment has been instituted. In most cases of toxic adenomatous goiter, iodine is of less value and there is some possibility that it may aggravate the condition.

It is impossible to give an entirely satisfactory explanation of the beneficial action of iodine in exophthalmic goiter. It is not, apparently, that the administered iodine is used for the conversion of an abnormal iodine-deficient hormone to a normal one, as Plummer suggested. Does the iodine act by stimulating the production of colloid which distends the alveoli and thereby blocks the pathways along which the hormone enters the blood stream? This is the view of Marine and is supported by the fact that a pronounced change in the consistency of the gland may frequently be noted immediately following iodine administration; the gland becomes firmer and tender to the touch (iodine thyroiditis) as a result presumably of the distension of the alveoli. Marine believes that when the colloid pressure attains a certain height *absolute* retention ceases, the discharge of the secretion being established at a higher level. This theory offers an explanation for the return of symptoms which frequently follows (in 2 or 3 weeks) the immediate beneficial effects of iodine. The *pressure-retention* conception also seeks to account for the usual failure of iodine to benefit the hyperthyroidism of toxic adenoma; the adenomatous alveoli seldom react by colloid accumulation.

It is probably the increased concentration of iodine in the blood which checks the liberation of the thyroid principle into the circulation and diverts it into the alveoli to be stored as colloid.

Thiourea and *thiouracil* lower the metabolic rate and have come into use in the treatment of thyrotoxicosis. Their action upon thyroid function is unique since in normal animals they cause *thyroid*

hyperplasia together with hypothyroidism. It is Astwood's view that they act by preventing the synthesis of thyroxine by the thyroid. They do not interfere in any way with the action of thyroxine upon the tissue cells because the usual increase in metabolism is observed when either of these drugs is administered with thyroxine. Nor is their effect upon thyroid function due to a relative iodine deficiency for it is not prevented by iodine administration. But these drugs prevent the development of hyperthyroidism which ordinarily results from the injection of thyrotropin and are ineffective in hypophysectomized animals. These observations lead to the conclusion that thiourea and thiouracil have a two-fold action, that they stimulate the production or liberation of thyrotropin by the pituitary which accounts for the thyroid hyperplasia, and also interfere with the production or the liberation of thyroxine. This latter effect explains the hypothyroidism and may be the primary and only direct action of these drugs, the outpouring of the pituitary principle being possibly a secondary or automatic response to the failure of thyroid function.

A consideration of factors other than an absolute iodine deficiency in the development of goiter

The work of McCarrison and others indicates that dietary factors, other than iodine deficiency, are also concerned in the production of goiter. Diets deficient in the fat-soluble vitamins and in vitamin C appear to be conducive to its development. The ingestion of excessive quantities of fat or of protein (especially of liver) also predisposes to it. In rabbits and rats, cabbage has been shown to be powerfully goitrogenic; cauliflower and Brussels sprouts have a similar effect. Iodine deficiency of the diet itself (absolute iodine deficiency) is not a factor in this goitrogenic effect. Drying the cabbage in a vacuum destroys its goitrogenic properties, whereas boiling it with hydrochloric acid does not. A characteristic of these vegetables is their relatively high content of cyanogen compounds. Taking this hint Marine and his associates gave various cyanides to rabbits and obtained a marked thyroid enlargement; methyl cyanide was especially effective. The thyroid hyperplasia was accompanied by exophthalmos.

Marine and his colleagues suggested that the goitrogenic effect of cyanides was dependent upon their property of depressing tissue oxidations, increased thyroid function being a compensatory reaction instituted to oppose this action. It was further suggested that exogenous or endogenous

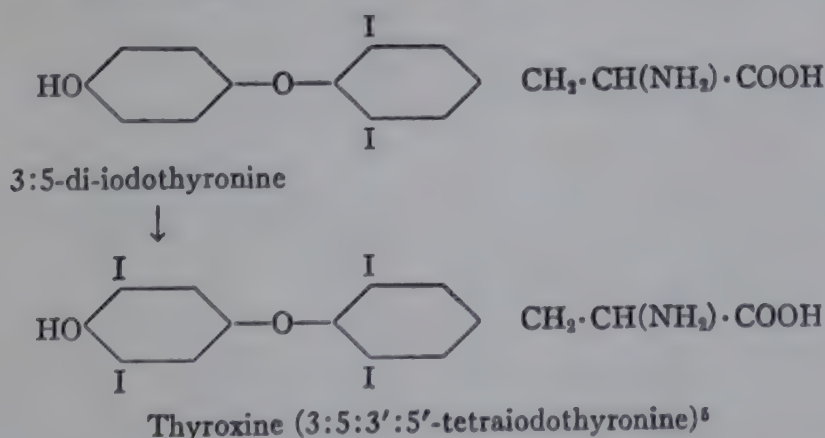
³ Iodine, 1 gram; potassium iodide, 2 grams; water, 30 cc.

cyanides or defective powers of the body to detoxicate such compounds might be a primary cause of exophthalmic goiter and that the compensatory reaction of the thyroid was brought about through the pituitary or the hypothalamic centers. It is more probable, however, that cyanides (also cyanates and sulphocyanates) exert their effect upon the thyroid either directly or through the pituitary, rather than by depressing tissue metabolism generally, for when a myxedematous patient, in whom the basal metabolic rate was maintained at near the normal level by thyroid administration, was given potassium sulphocyanate daily for six weeks, no reduction in metabolism resulted. This shows that the action of the thyroid principle upon the tissue cells was not impaired. On the other hand, cyanate given to a person with normal thyroid function causes a fall in the basal metabolic rate,—presumably by suppressing the liberation of thyrotropin.

The possibility of infected drinking water, in some instances, playing a rôle in the development of goiter has been mentioned (p. 677). All the factors cited in this section apparently act indirectly, the goitrogenic effect being brought about through the production of a *relative* iodine deficiency, i.e., through the creation of a greater demand for iodine; or, possibly in some instances, through interference with the absorption of iodine. The effects can be counteracted by iodine administration.

THE THYROID HORMONE

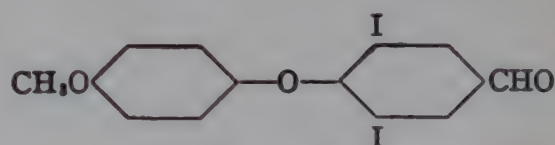
A glycerine extract of sheep's thyroids was first employed successfully by the English physician George Murray in 1891 for the relief of myxedema. The thyroid tissue itself when given by mouth was shown subsequently to be physiologically active.



believed that the iodine was present in organic combination and named the compound *iodothyrim*. It was shown subsequently by Oswald (1899) that the active iodine constituent was attached to a protein—*thyroglobulin*—which is the chief component of the colloid material filling the alveoli of the gland.

The active principle of the thyroid was isolated in crystalline form by Kendall in 1919. He named the substance *thyroxin*⁴ and found that it contained 65 per cent of iodine and an amino group. Harington and Barger in 1927 established the chemical formula of thyroxine and effected its synthesis. It was found to be constituted of 2 benzene rings united by an oxygen bridge, and to contain 4 atoms of iodine and an amino-acid side-chain. The synthesis required a number of separate steps.

3:5-di-iodo-4-(4'-methoxyphenoxy) benzaldehyde contains iodine atoms in the same positions as two of those in natural thyroxine—



3:5-di-iodo-4-(4'-methoxyphenoxy) benzaldehyde

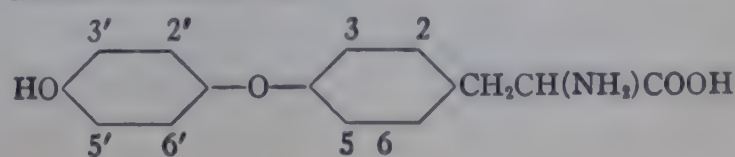
This compound having been prepared, the amino group was attached by condensation with hippuric acid. The resulting compound was boiled with NaOH in alcohol and then with acetic anhydride and hydriodic acid. The product of these procedures,—*3:5-di-iodothyronine*—, readily takes up 2 additional atoms of iodine with the formation of thyroxine, when treated with a concentrated solution of iodine in potassium iodide.

Thus—

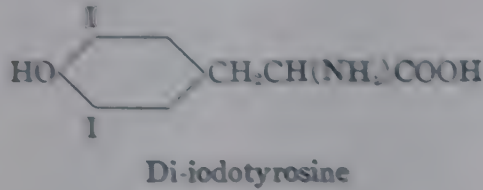
Baumann in 1896 discovered that iodine was an important constituent of the thyroid extract. By acid hydrolysis of thyroid tissue and later by peptic digestion he obtained a brownish powder containing 10 per cent of iodine and possessing the physiological activity of the whole gland. He

⁴ Now usually spelled thyroxine.

⁶ The numbering of the positions in the thyronine nucleus are shown below.



Synthetic thyroxine possesses physiological properties identical with those of the natural product. Thyroxine is related to tyrosine. Only 40 per cent or so of the iodine in the thyroid is contained in the thyroxine molecule, the remainder is present in di-iodotyrosine:



This compound is formed in the body from tyrosine and almost certainly represents a stage in the synthesis of thyroxine; when added to slices of surviving thyroid tissue di-iodotyrosine is converted to thyroxine. Di-iodotyrosine itself has only slightly physiological activity.

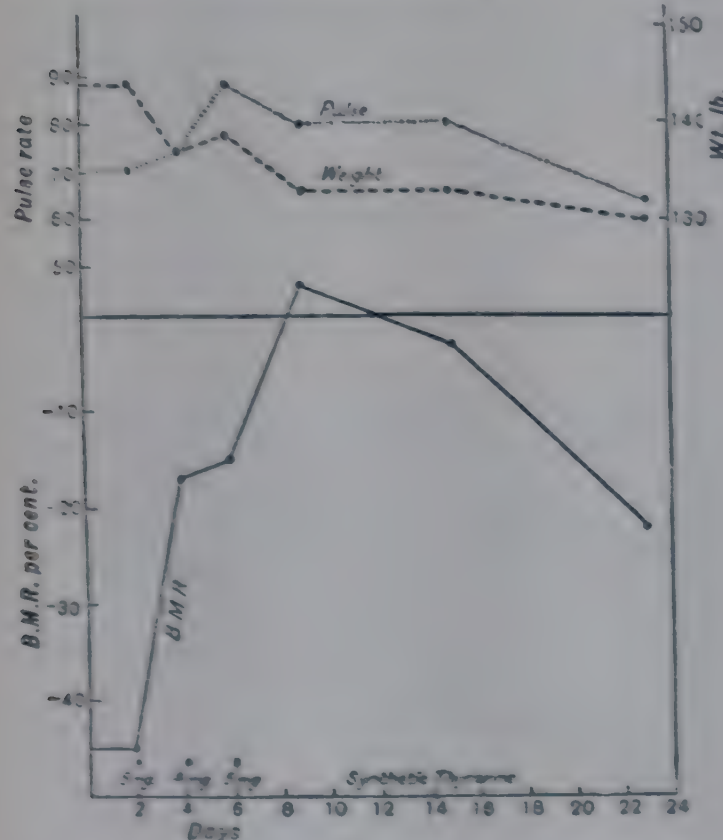


FIG. 267. Effect of thyroxine on a myxedematous patient. (After Harington.)

Before leaving the subject of thyroxine synthesis, two rather astonishing discoveries should be mentioned. A substance identified chemically and physiologically as thyroxine has been obtained by the hydrolysis of iodinated casein with alkali and heat (Ludwig and Mutzenbecher); and the feeding of iodinated serum protein to hypothyroid subjects raises the metabolic rate and relieves the symptoms (Lerman and Salter).

It is very unlikely that thyroxine is identical with the hormone discharged from the thyroid into the blood

stream. Its very low solubility argues against thyroxine being the hormone itself. Moreover, the activity of thyroglobulin (or of the dry gland) is greater than can be accounted for by its free thyroxine content. Thyroglobulin activity is more closely related to total iodine content. A conception which fits the facts best is that di-iodotyrosine and thyroxine are linked together to form a peptide which, combined with other amino-acids, is built up into thyroglobulin (colloid). The disruption of the thyroglobulin by laboratory procedures the highly active peptide is split into the active thyroxine and the inactive di-iodotyrosine. When, on the other hand, thyroglobulin undergoes natural breakdown, the intact peptide which, according to the present conception, is the true hormone, is released into the blood stream.

The action of the thyroid hormone

The thyroid hormone is believed to act as a catalyst to increase the oxidative processes of the tissues or at least to increase the activity of the respiratory enzymes in the cells. The oxygen consumption of tissue excised from a hyperthyroid animal is normal, whereas the metabolism of tissue removed from a hyperthyroid animal is greater than normal. These observations indicate, of course, that the action of the thyroid hormone is exerted directly upon the cells rather than through the nervous system. The effect of a single administration of thyroxine upon the basal metabolic rate is slow to develop and lasts for a long time (fig. 267). It commences after the lapse of about 7 hours, reaches its maximum in from 8 to 10 days and lasts for 6 weeks. Thyroxine brings about the conversion of a relatively enormous quantity of material. 1 mg. causes the total CO₂ output to increase by some 400 grams and elevates the basal metabolic rate by 2.5 per cent. The entire normal adult human body contains about 14 mg. of thyroxine. It has been calculated that the gland maintains this amount constant by manufacturing and delivering about 0.33 mg. per day. In other words, 0.33 mg. of the hormone is consumed daily, and as a matter of fact the daily quantity of administered thyroxine required to maintain the metabolism of a thyroidless adult at the normal level has been found to be about 0.5 mg. Animals when given repeated doses of dried thyroid, or of pure synthetic thyroxine, develop the features of hyperthyroidism, e.g., raised metabolic rate, weight loss, increased excretion of nitrogen and of calcium (chiefly in the feces) reduction of liver glycogen, tachycardia, etc. The coincident administration of amino-acids enhances these effects. The administration of dried thyroid substance by

The form of compressed tablets is a complete substitute for myxedema. Cretinism also, if discovered early, can be immensely improved, and almost normal bodily and mental development secured (figs. 263 and 264). Thyroxine is equally effective. The latter, in that it is a chemically pure substance and so can be accurately measured, possesses an advantage over the dried gland, which is variable in potency.⁶ Nevertheless, thyroxine has the greater disadvantage of being less potent and possessing a less certain action when given by mouth. This is due to its relative instability and its imperfect absorption from the

THE SECRETION OF THE THYROID HORMONE

The thyroid cells under ordinary circumstances discharge their secretion into the alveolar lumen. As, just mentioned, it is stored until required. According to one view, the stored material is then picked up again by the cells of the alveoli and passed into the blood stream. Other investigators believe that the hormone finds its way into the blood vessels via channels between the cells. The first mentioned view is held by Severinghaus who describes the cells as sending pseudopodia-like processes into the colloid which they are believed to absorb and transfer to the blood. When the demand for hormone is great and the reserve store exhausted, the cells may then pass their secretion directly into the circulation.

Though nervous impulses may play some part in regulating the production and liberation of the

A given extract may be assayed either *chemically*, by determining its content in iodine bound in thyroxine according to the method of Harington and Tall or *biologically*. Several biological tests have been used, e.g., the rate of carbon dioxide production in man, the rate of oxygen consumption of rats, or the increased sensitivity of the latter animals to oxygen deficiency, and finally the tadpole test of Gudernatch, in which the rate of metamorphosis is taken as the criterion. The last mentioned test is, however, dependent upon the total iodine content of the specimen (p. 572) and as we know, only a part of this is active in mammals. Axolotls have been used for a similar purpose. Thyroid feeding renders mice less susceptible to poisoning by acetonitrile (Reid Hunt). This fact has also been used as a basis for testing the potency of thyroid preparations.

thyroid hormone, it is now generally accepted that the chief and essential mode of control is by the thyrotropic principle of the anterior lobe of the pituitary (p. 725). Thyroid tissue has been shown by *in vitro* experiments to inactivate the pituitary principle. Reactivation can be brought about by means of heat. The hormone in inactivated form is excreted in the urine of normal persons and of subjects of thyrotoxicosis, and can be detected by heating the urine. In myxedema, active thyrotropin is excreted. It is not improbable that a high concentration of the thyroid hormone in the circulation causes in some way inactivation of the thyrotropic hormone and, thus, an automatic control is exerted over the action of the pituitary principle. There is also evidence that an excess of the thyroid hormone in the blood depresses the output by the pituitary of thyrotropin. On the other hand, thyroglobulin has been found to depress the oxygen consumption of the thyroid which suggests an additional means by which thyroid activity is automatically controlled.

The dispensibility of the thyroid for the synthesis of thyroxine

The surprising discovery has been made that the thyroidless animal can synthesize thyroxine. Morton and his colleagues fed radioactive iodine to rats and recovered radioactive thyroxine later from their bodies. This observation coupled with the fact already mentioned, that iodinated protein possesses thyroxine-like activity, has aroused the speculation that lower forms of animal life, which do not possess a thyroid, utilize as stimulants to metabolism, iodinated protein compounds in their food. If it were possible to obtain a sufficient quantity of such compounds in the diet, higher animals also could probably dispense with the thyroid gland. The thyroid thus is seen as a highly specialized structure which more active forms of life have evolved for the conversion of compounds of low activity formed in the tissues generally, into a principle whose potency has been multiplied a hundred-fold over that of the original material.

CHAPTER LIX

THE ADRENAL GLANDS (SUPRARENAL CAPSULES)

Development and structure

The mammalian adrenal gland, like the pituitary body and the thyroid-parathyroid apparatus, consists of two parts which, though closely associated anatomically, have separate origins, are structurally different and so far as is known, functionally independent. The central part of the gland is called the *medulla*; the outer enveloping rim of tissue is known as the *cortex*. In certain fishes (Elasmobranch) the analogues of these two parts are not joined together. Tissue corresponding to the mammalian medulla, for example, is found as a number of small discrete masses on either side of the spine in association with the sympathetic ganglia, while an elongated structure lying between the kidneys (*inter-renal body*) corresponds to the adrenal cortex of mammals. In the amphibia and reptilia the two types of tissue have come together, but masses of cortical cells are intermingled with islets of medullary tissue and the two tissues are not segregated into a peripheral and a central zone, as in the mammalian adrenal.

The medullary cells exhibit characteristic staining reactions; ferric chloride turns them blue, osmic acid black, and chromic acid or its salts a dark brown. As a result of the last mentioned reaction they are spoken of as chromophil or chromaffin cells.

In all animals the medullary tissue and the sympathetic ganglion cells have a common origin; they develop from primitive cell masses which have separated from the neural crest. Migrating from their sites of origin these masses of ectoderm cells undergo differentiation along two paths, some into sympathetic ganglion cells, others into chromaffin tissue. In the abdomen on either side of the mid-line a relatively large mass of chromaffin cells becomes enveloped by cortical tissue to constitute the adrenal medulla. Other smaller masses persist as accessory chromaffin tissue in association with the ganglia and plexuses¹ of the sympathetic. On the other hand, sympathetic ganglion cells may be found scattered among the cells of the adult adrenal medulla. The cortex is developed from mesoderm. It arises as a bud from the celomic epithelium covering the inner side as the fore part of the mesonephros. The celomic epithelium immediately behind this area gives rise to the germinal epithelium from which in turn the sex glands develop.

The medulla is composed of closely packed groups of polyhedral cells containing chromaffin granules which are looked upon as the mother substance of the medullary secretion. The cell groups are separated by blood sinuses which empty into a central vein. The cells of the cortex are arranged in three zones. These are from without inwards the (1) *zona glomerulosa*, in which

groups of cells are arranged in a circular or oval pattern, (2) *zona fasciculata*, in which the cells are arranged in columns, and (3) *zona reticularis*, which is composed of a network of cell cords (fig. 268). The cells of the cortex contain fine droplets of doubly refracting lipid material which is also seen in the form of dust-like particles in the capillaries of this part of the gland; it probably is the active cortical hormone or its precursor.

The cells of the cortex originate at the periphery of the gland, in the *zona glomerulosa* just beneath the capsule, or more probably from the cells of the capsule itself. These young cells contain numerous mitochondria but relatively little lipid material. As the cells become older they migrate towards the medulla of the gland, the mitochondria become fewer and the lipid material more abundant. The lipid diminishes again later; the migrating cells become shrunken in appearance and finally die near the cortico-medullary junction. The lipid droplets contain cholesterol and insoluble ketones. The mitochondria are believed to be concerned in the production of the cortical hormone. Hypertrophy and hyperactivity of the adrenal cortex (induced by corticotropin p. 726, or by removal of one adrenal) is associated with proliferation of the mitochondria and a decrease in the lipid material. Adrenal atrophy (as follows hypophysectomy) is accompanied by a decrease in mitochondria and the lipid material appears to be increased due to its accumulation into larger droplets clumped together.

On the basis of lipid distribution, the normal adrenal cortex has been divided by Weaver and Nelson into four zones—an *outer zone*, comprising the *zona glomerulosa* and poor in lipid material, a narrow *optically inactive zone*, between the *zona glomerulosa* and the *zona fasciculata*, an *optically active zone* the richest in lipid material its cells being well-filled with fine dust-like particles, and an *inner zone*, relatively poor in lipid and comprising the *zona reticularis* and a small part of the *zona fasciculata*.

Blood and nerve supply

The adrenal is one of the most richly vascular organs in the body, receiving 6 to 7 cc. of blood per gram of tissue per minute. It is supplied by 3 small arteries which are derived, respectively, from the inferior phrenic artery, the renal artery and the aorta. They form rich plexuses in the cortex. The plexuses are continuous with the sinuses of the medulla which drain into the central vein of the latter. The right adrenal vein empties directly into the inferior vena cava. The left vein into the renal vein. The nerves are derived from the great splanchnic, the fibers pass through a plexus (suprarenal) before entering the gland.

¹ Such chromaffin collections are called *paraganglia*.

bers are medullated and have no cell stations in their course. That is, they are entirely preganglionic, the medullary cell itself taking the place of the ganglion cell and postganglionic fiber; they differ thus from all other sympathetic pathways (see p. 948).

THE ADRENAL MEDULLA

Thomas Addison's report in 1855 (p. 697) and the experimental work of Brown-Séquard in 1856 gave the first hints concerning adrenal function. The last-mentioned observer showed that complete removal of the glands from rabbits caused death. The French physiologist Vulpian in the same year discovered that the medulla, unlike any other tissue, was stained blue by ferric chloride, and that the blood of the adrenal vein sometimes gave a

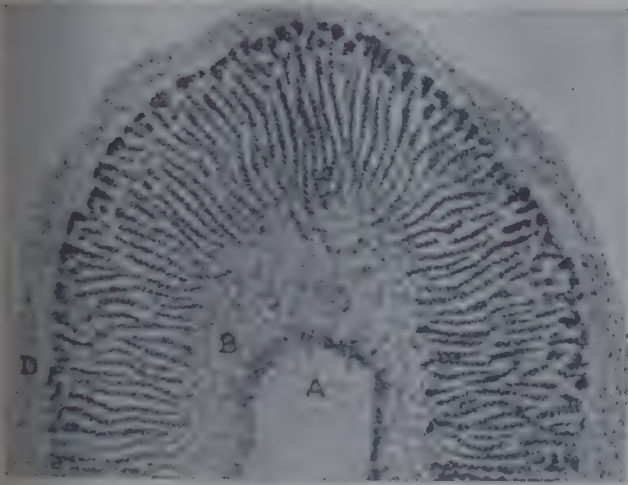
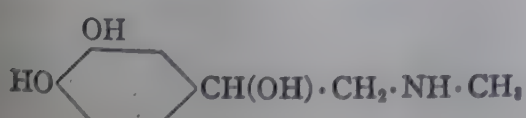


FIG. 268. Section of the human suprarenal capsule. A, medullary portion; B, zona reticularis; C, zona fasciculata; D, capsule; the zona glomerulosa is situated just beneath the capsule. (After Maximow and Bloom.)

similar reaction. The staining reaction, it is now known, is characteristic of the internal secretion of the medulla (adrenaline). In 1894 Oliver and Schafer obtained an extract from the medulla which upon injection caused a pronounced rise in blood pressure. The active principle of the extract was obtained in pure form in 1901 by Takamine and by Aldrich. Upon analysis the latter observer found the empirical formula to be $C_9H_{17}O_2N$. The substance has been given various names—adrenaline, (or adrenalin) epinephrine, adrenin and suprarenin. The first of these names is most commonly used. Adrenaline is closely related to tyrosine, as will be seen from the following structural formula:



Adrenaline is a secondary alcohol, its full chemical name being 3,4-dihydroxy- α -phenyl- β -methylamino-ethanol. It was first prepared synthetically by Stoltz (1904) and later by Dakin (1905). Adrenaline possesses an asymmetric carbon atom, so three isomers are possible (i.e., a levo- and a dextro-rotatory and a racemic form). The natural levo compound is 15 times more powerful than the dextro-rotary. Tyrosine is a probable precursor of adrenaline. The introduction of a second HO group into the tyrosine molecule can be effected by the enzyme tyrosinase present in plants; dioxyphenylalanine (dopa) is formed. Tyrosinase is not found, however, in animal tissues, but it has been shown that dopa can be produced from tyrosine by the action of ultraviolet light in the presence of Fe^{++} ions or ascorbic acid.

THE ACTION OF ADRENALINE

The actions of pituitrin and adrenaline possess certain features in common. They both stimulate the uterine muscle and raise the blood pressure by constricting the vessels. The effects of the two differ, however, in that pituitrin action bears no relation to the sympathetic innervation of the structures acted upon, whereas adrenaline acts only upon structures receiving sympathetic innervation and in a manner corresponding to the action of the sympathetic fibers themselves. In general, its effects imitate almost perfectly those evoked by stimulation of the sympathetic system. Its action therefore is said to be sympatho-mimetic. Adrenaline, for instance, inhibits the muscle of the bowel, pituitrin causes excitation; the latter causes constriction of the coronary vessels, the former dilatation. Yet adrenaline does not act upon the sympathetic nerve endings themselves since its effects are not reduced (indeed they are magnified) by section and degeneration of the nerves (p. 947). It is said to act upon the hypothetical substance in the muscle or gland (*receptive substance of Langley*) in which the nerve fibers terminate.

The effects of adrenaline administration are of shorter duration than those of pituitrin. The pressor effect induced by the former does not persist for more than a minute or two. Adrenaline disappears rapidly after injection, due it is supposed to its oxidation in the tissues. The effects following subcutaneous injection are much less intense, though more prolonged, than those induced by intravenous administration. When given orally adrenaline is inert. Adrenaline is rapidly inactivated in the body. The site of inactivation is mainly in the liver, though the process also occurs in other tissues. Yet outside

the body adrenaline is much more stable in blood and tissue fluids than in Ringer solution, in which it undergoes oxidation to form a red compound. The substances in blood and tissue fluids which have a stabilizing or protective action upon the adrenaline molecule are reducing agents, such as glutathione and ascorbic acid (Welch). It is significant that the adrenal gland is especially rich in these substances.

The actions of adrenaline will be considered under the following headings:

(a) *Circulatory*

In amounts which may be considered within physiological limits (about 0.01 cc. per kilogram of 1 in 10,000 solution administered subcutaneously) adrenaline shows a differential action upon the vessels. The arterioles and capillaries of the skin, mucous membranes and splanchnic viscera (except the intestinal vessels which usually dilate) are constricted; the vessels of the muscles at the same time dilate. With such a dose the constrictor overshadows the dilator effect, the net result being a rise in blood pressure. The coronaries are dilated. Thus, there occurs a redistribution of blood, which is moved from the splanchnic area and skin to the skeletal and cardiac muscles. The vessels of the lungs are little affected, or dilated, by such doses; larger injections cause pulmonary vasoconstriction. The arterioles of the brain are dilated passively by the general rise in blood pressure (p. 292).

It is evident from the foregoing that adrenaline does not, as is often assumed, cause general vasoconstriction. Certain vessels, such as the coronaries, intestine and probably also the vessels of the skeletal muscles, according to Dunlop, are dilated even by relatively large doses of adrenaline. The vessels of the skin and of the splanchnic viscera with the exception of the intestine are constricted by any effective dose.

In very small amounts (0.01 cc. per kilogram of 1 in 50,000 or 1 in 100,000 solution) a fall in blood pressure (*depressor effect*) results. This is attributed to the dilator response in the muscles overbalancing the vasoconstriction in the skin and abdominal organs. A pressor effect, however, may be obtained even with these small doses if the blood pressure is already low or the animal under deep anesthesia. On the other hand, a depressor effect is obtained with large doses if ergotoxine (or ergotamine) an active principle of ergot, has been given previously (fig. 269). Ergotoxine, it is believed, paralyzes the vasoconstrictor

mechanism but leaves the vasodilator intact. It was shown by Hartman and Kilborn in kittens that the vasodilator effect of adrenaline is absent at birth and does not develop fully until the animals are about 11 weeks old.

In animals the *heart* is slowed by adrenaline if the vagi are intact; its beat is strengthened. The slowing is a reflex effect (through sinus and aortic nerves) of the elevated blood pressure, and does not occur if this is kept low by bleeding. Increase

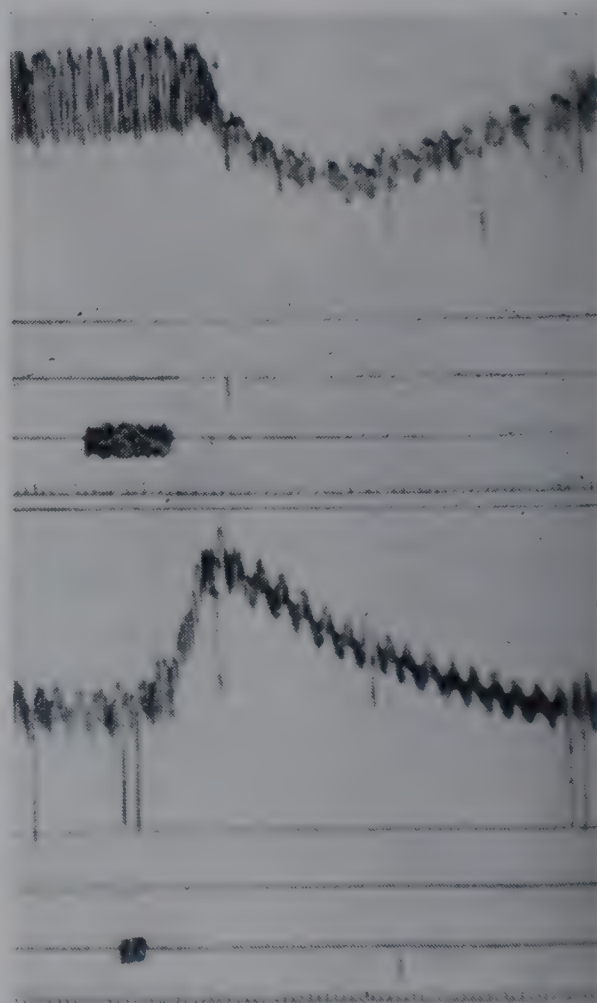


FIG. 269. Lower tracing shows effect of intravenous injection of 0.02 mg. adrenaline upon blood pressure. Upper tracing from the same animal shows the fall in pressure produced by the injection of 0.02 mg. of adrenaline following a previous dose of 0.4 mg. per kilogram of ergotamine tartrate. (After Geiling.)

of both the rate and force of the heart result if the vagi have been cut previously or their effects abolished by atropine. When given subcutaneously (0.5 cc. of the 1:1000 solution) to the human subject, adrenaline quickens the heart rate. Adrenaline greatly increases the oxygen consumption of cardiac muscle.

(b) *Plain muscle*

Adrenaline inhibits the muscle of the stomach, intestine, bronchioles and wall of the urinary bladder.

Both the tone and movements of the intestine² are inhibited (fig. 270); the bronchioles are dilated. It excites the muscle of the gall-bladder, ureter, trigone and sphincter of the bladder, the retractor penis and the pyloric, ileocolic and internal anal sphincters. The uterus, whether pregnant or non-pregnant, is contracted in many animals, but in the cat, rat, mouse, guinea pig and man, the pregnant organ alone is contracted by adrenaline, the non-pregnant is inhibited. As a result of the excitation of the radiating fibers of the iris (dilator pupillae) the pupil is dilated by adrenaline especially if the superior cervical ganglion has been

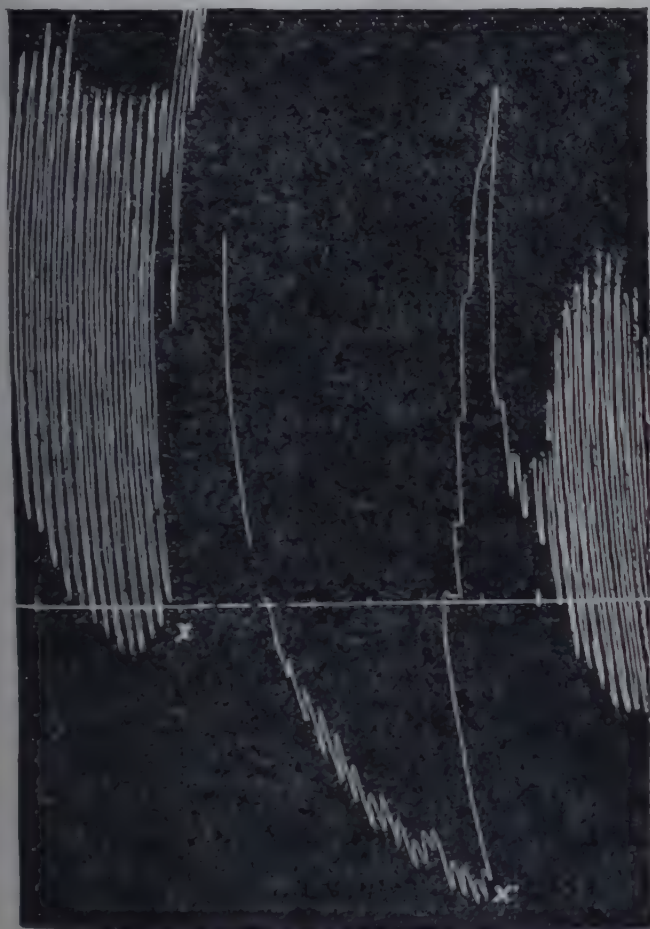


FIG. 270. Rabbit's intestine in Ringer's solution. At X Ringer's solution + adrenaline 1:100,000,000; at X' Ringer's solution substituted. Time 30 sec. (After Hoskins.)

previously excised. *Mueller's muscle* is stimulated and the eyeball protruded. Retracting of the upper eyelid is caused by the stimulation of its smooth muscle. The *nictitating membrane* of animals is retracted. Adrenaline also stimulates the *erectores pilae muscles* and other smooth muscle fibers in the skin.

(c) Skeletal muscle

Fatigue of skeletal muscle is postponed. The intramuscular injection of adrenaline increases an

² A dilution of adrenaline as high as 1 in 400,000,000 causes inhibition of the intestine. A dilution greater than this causes augmentation (Hoskins).

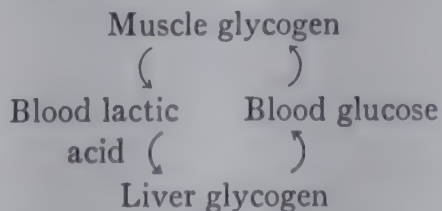
animal's capacity to perform work. (See fig. 344, p. 826.)

(d) Respiration

After a short initial period of apnea the respirations are increased in rate and depth. The apneic period is apparently secondary to the rise in blood pressure and is brought about through the carotid sinus mechanism (p. 346).

(e) Metabolism

(1) *Carbohydrate metabolism.* Adrenaline administered by injection causes hyperglycemia and glycosuria. It shows an antagonism to insulin—relieving hypoglycemic convulsions. These effects are due to the mobilization of sugar from the liver whose glycogen stores are thus reduced. The hyperglycemic effect is therefore greatest in well-fed animals with an abundant hepatic store of carbohydrate, and of course is not obtained in hepatectomized animals. The glycogen of the muscles is also reduced by adrenaline. On the other hand, there is evidence (Himsworth and Scott) that the rate of removal of glucose from the blood by the tissues is accelerated. When administered to animals after a prolonged fast or in other conditions which deplete the hepatic glycogen stores, adrenaline causes an increase in liver glycogen. The latter is due to the breakdown of muscle glycogen to lactic acid which, diffusing into the blood, is carried to the liver where re-synthesis to glycogen occurs. There is a fall in the inorganic phosphate of the blood due apparently to the phosphorylation of glycogen and the formation of glucose monophosphate. If the adrenaline administration is continued the liver glycogen is converted in turn to glucose which passes into the blood, causing hyperglycemia; it is subsequently reconverted to glycogen in the muscles (Cori). The cycle may be represented in the following scheme:



(2) *General metabolism.* Oxygen consumption is increased by from 20 to 40 per cent, and CO₂ production by from 30 to 50 per cent; the respiratory quotient is therefore raised. In man the increase in the basal metabolic rate occurs within a short time after the subcutaneous injection of

0.5 cc. of a 1:1000 solution; the temperature of the muscles rises. The effect of adrenaline upon heat production has been called by Boothby and Sandiford its *calorigenic* action. The effect is believed by these workers to be partly the result of the hyperglycemia (carbohydrate plethora) and partly to a direct stimulating action upon cellular oxidative processes; it does not occur after removal of the liver (Soskin). The calorigenic effect is not brought about through an action upon the thyroid since it is obtained after thyroidectomy. Moreover the rise in metabolic rate commences within a few minutes and returns to normal within 2 hours or so, whereas the effect of thyroxine upon heat production does not commence for some hours and is prolonged for many days (p. 682). Definite circulatory and respiratory effects accompany the increased heat production. The systolic pressure rises, the diastolic pressure falls. The heart rate and the cardiac output are increased. The respiratory rate and total pulmonary ventilation are raised.

The dose of adrenaline required to produce a detectable metabolic response (rise in blood sugar and in metabolic rate) is considerably less than that which will cause a rise in blood pressure. Also, because of its rapid inactivation in the body, a given dose of adrenaline has a much greater effect upon metabolism if administered continuously over a period than if given in a single injection.

(f) Other effects of adrenaline

(1) Secretion of saliva;¹ (2) lacrymation; (3) sweating in such animals as horses and sheep, but in most other animals and in man the sweat glands, though innervated by the sympathetic, are not excited by adrenaline (see p. 627); (4) contraction of the spleen (stimulation of the smooth muscle of its capsule and trabeculae) and consequent increase in the blood volume and in the red cell count (p. 54); (5) increase in the coagulability of the blood; (6) small doses increase the flow of urine as a result of constriction of efferent glomerular vessels; larger doses constrict both afferent and efferent vessels and through reduction of the renal blood flow diminish the urinary flow (p. 387); (7) a fall, sometimes preceded by a rise, in the potassium of the blood; (8) contraction of melanophores of certain cold-blooded animals, e.g., frog and horned toad (Redfield).²

¹ The contraction of the melanophores of the horned toad which results from adrenal administration occurs when the animal becomes excited. Since in the latter

THE EFFECTS OF CERTAIN SUBSTANCES
ACTION OF ADRENALINE. Ergotoxine or *ergometrine* annuls the excitatory (motor and secretory) of adrenaline or of sympathetic stimulation. Inhibitory effects, e.g., vasodilator, are not interfered with. For this reason certain effects of adrenaline action or of sympathetic stimulation appear unaltered or reversed by *ergometrine*. Thus, as already mentioned, a depressor effect is obtainable with adrenaline if *ergometrine* has been administered previously. After *ergometrine*, adrenaline causes expansion of melanophores of the frog instead of the usual contraction. The hyperglycemic response to adrenaline is abolished after *ergometrine*. A *potentilla* is one which reverses or annuls some of the effects of adrenaline whereas *coumine* enhances its vasoconstrictor, cardiac and pupillary reactions. In their effect on the capillaries, blood pressure and bronchioles, histamine and adrenaline are antagonistic, and adrenal animals show an increased susceptibility to histamine administration. The blood-concentrating effect of histamine administration is lessened or prevented by previous injection of adrenaline. There is no evidence that histamine increases the output of adrenaline from the medulla.

ADRENALINE-LIKE SUBSTANCES. *Ephedrine* isolated by Chen in 1924 from the Chinese plant *Ephedra*. Its chemical resemblance to adrenaline makes it from the formula:



Ephedrine 1-phenyl-3-methylamino propan-2-ol

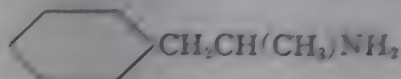
This alkaloid is closely similar to adrenaline in its action, causing bronchial relaxation, vasoconstriction, hyperglycemia, inhibition of intestinal peristalsis, excitation of other smooth muscle. It has a calorigenic action, its pressor effect (Cushing) is annulled by *ergometrine* and reduced by *coumine*. It is about 1000 times less powerful than adrenaline and its effects are more prolonged. Because of its pressor effect it is often combined with adrenaline in commercial preparations. Unlike adrenaline it is not taken by mouth, 50 to 150 mg. has produced rise in blood pressure. Tyrosine is formed by the action of bacteria on *tyrosine* (decarboxylation of tyrosine). It is also in the salivary glands of certain molluscs. It is called an *adrenalin* and resembles in some of its actions, e.g., it elevates the blood pressure and stimulates the uterine muscle. Its formula is:

instance the effect is abolished if the adrenal medulla is removed but not when the adrenal glands are not, the effect must be due to a rise in the blood pressure—presumably adrenaline—in the blood.



ine (4-hydroxy- α -phenyl- β -amino ethane)

is another substance closely allied chemically to adrenaline, as shown in the following formula:



phenedrine (α -phenyl- β -amino propane)

This compound has a stimulating action upon the nervous processes somewhat like that of caffeine, inducing alertness, postponing mental fatigue and relieving nervous depression.

Some skins of certain toads secrete substances (*bufotoxins* and *bufoteninedine*) similar in action to adrenaline; the secretion of these substances is increased during excitement.

EMPLOYMENT OF ADRENALINE IN MEDICINE.

Adrenaline is used: (a) to staunch bleeding from accessible surfaces (epistaxis, hematemesis) or from

On account of its pressor effect it is of no value and may do harm in pulmonary hemorrhage and in cases of internal bleeding. (b) To shrink mucous membranes, especially of the nose, and is then frequently in combination with ephedrine. (c) To relax the muscles of the bronchioles in asthma; the relief following its use is very striking. (d) To combat certain allergic reactions, e.g., serum sickness, and to antagonize the action of the histamine-like substances supposedly present in the skin in such conditions as urticaria and angioedema. (e) To stimulate the respirations or to restart the heart which has ceased to beat; in the latter event it may be given by injection into the cardiac muscle. Adrenaline is of value in syncope due to Adams disease (p. 192). It should be mentioned that the administration of adrenaline during general anesthesia is attended by the danger of inducing ventricular fibrillation (p. 198). (f) To enhance and prolong the action of cocaine and similar anesthetics; the vasoconstriction thus induced retards the absorption of these substances, thus prolonging their effects and reducing their toxicity. It is also used as an aid in spinal anesthesia.

BIOLOGICAL TESTS FOR ADRENALINE

Intestinal segment. The fluid suspected of containing adrenaline (blood, serum, etc.) is applied to a segment of surviving rabbit intestine. Inhibition of the peristaltic movements will result if the fluid contains adrenaline. An estimation of the adrenaline concentration in the fluid may be arrived at by matching its effect with that of an adrenaline solution of known concentration.

Segment of the non-pregnant uterus of the rabbit. Employed in a similar manner. This test is also used in the presence of adrenaline.

(c) *Isolated arterial rings.* A ring of a small artery known to react to adrenaline by constriction is suspended in Locke's solution. The arterial ring is attached by a thread to a lever applied to a smoked surface. The fluid to be tested is added to the bath in which the arterial ring is immersed.

(d) *The denervated iris.* Removal of the superior cervical ganglion renders the pupil highly sensitive to the dilator action of adrenaline (the paradoxical pupillary reaction of Meltzer). The fluid to be tested is instilled into the conjunctival sac of an animal so prepared.

(e) *The caval pocket method of Stewart and Rogoff.* This is an auto-assay method. The liberation of adrenaline is demonstrated through its action upon the denervated iris. The inferior vena cava is clamped below the entrance of the adrenal veins and again just below the diaphragm. All veins entering this caval pocket, except the adrenal veins, are ligated. After a measured period of time the upper clamp is removed; dilatation of the pupil results if adrenaline has been secreted in the interval between the closure and opening of the upper clamp. In quantitative determinations the lower clamp is removed and the blood collected through a cannula inserted into the vein. The concentration of adrenaline in the collected blood is then estimated from tests upon a segment of beating intestine.

The denervated heart (described on p. 690).

THE SECRETION OF ADRENALINE

The secretion of adrenaline is under nervous control. Whether or not adrenaline is discharged continuously into the blood stream under ordinary circumstances is a debatable question. Stewart and Rogoff estimated that in anesthetized animals the glands discharged 0.0002 mg. of adrenaline per kilogram of body weight per minute. But, since anesthesia and operative procedures stimulate the adrenal medulla, such experiments do not settle the question of a spontaneous liberation of adrenaline under normal conditions. During rest and under physiological conditions the concentration of adrenaline in the blood is probably not greater than from 1:2,000,000,000 to 1:1,000,000,000 (Rogoff). Such a high dilution has no demonstrable effect in the intact normal animal. On the other hand, Cannon and Rapport found that in states of stress (see emergency function, below) or during splanchnic stimulation, the output of adrenaline amounted to from 0.003 to 0.004 mg. per kilogram per minute. Reduction or exhaustion of the adrenaline content of the gland results from stimulation of the great splanchnic nerve, puncture of the floor of the fourth ventricle or reflexly from excitation of a sensory nerve. The adrenaline

liberation caused by one or other of these procedures may cause an increase in metabolism of over 20 per cent. Anesthesia, asphyxia, strenuous exercise, etc., or the administration of such drugs as strychnine, nicotine and morphine also cause the secretion of adrenaline if the nerves to the glands are intact, but not after the gland has been completely denervated. Massage of the adrenal also causes the passage of adrenaline into the blood stream. Cannon and Rapport place the center for the control of adrenal secretion in the upper part of the floor of the fourth ventricle. This is probably not the highest center since stimulation of the hypothalamus will cause a discharge of adrenaline. The concentration of adrenaline in the resting gland is about 0.1 per cent of its moist weight and the total store in both adrenals of man is about 10 mg. High temperature and infections are said to cause a reduction of the adrenaline store.

THE RÔLE OF THE ADRENAL MEDULLA IN THE BODY

That the effects of adrenaline when administered by injection represent the physiological actions of the medullary secretion in the living body are strongly suggested by the following facts: (a) The almost perfect correspondence between the effects of adrenaline administration and those resulting from the stimulation of different nerves of the sympathetic system; (b) the common origin of the adrenal medulla and the sympathetic nervous system; (c) the discharge of adrenaline into the blood stream under the experimental conditions mentioned above and the researches to be immediately described.

The adrenal medulla is not essential to life. In animals one adrenal may be removed completely and the medulla of the other excised without any apparent ill effect—the animal survives the operation indefinitely.

The emergency theory of adrenal function

Cannon and his colleagues have furnished convincing evidence that the medulla liberates its secretion in significant amounts only under conditions which call for unusual effort on the part of the body to perform work, to prevent changes in its internal environment or to resist threatened dangers. In such times of stress the medullary secretion, it is believed, reinforces the sympathetic nervous system. Through this hormonal-nervous cooperation the several bodily reactions associated with such states of emergency are raised to maximal efficiency. Cannon and his

associates employed the denervated heart as an indicator of adrenaline liberation. The operation for denervation comprises section of the vagi and removal of the stellate and second thoracic ganglia of the sympathetic chain; the heart is thus completely isolated from nervous control. Since in their experiments any effect due to a change in the temperature of the blood was excluded, a pronounced acceleration of a heart so prepared was taken to be the result of a chemical substance carried in the blood stream. Fright, rage, pain, asphyxia, anesthesia, metabolites resulting from muscular activity, exposure to cold, stimulation of a sensory nerve and several other conditions, caused within 10 seconds an increase in heart rate of from 20 to 40 beats per minute. Removal of the adrenals, their denervation, or ligation of the adrenal veins, prevented this effect. The conclusion, therefore, is justified that the various conditions mentioned cause the reflex liberation of the medullary hormone. The denervated heart responds to as little as 1 part of adrenaline in 1400 million parts of blood. In some of Cannon's experiments, cats were frightened by the barking of a dog; the rate of the denervated heart increased by from 15 to 30 beats per minute. The cardiac acceleration was accompanied by pupillary dilation, erection of the hairs and spitting. When motor activity, e.g., struggling in the animal holder, accompanied the emotional excitement the cardiac acceleration was more pronounced (40 to 80 beats per minute). Even minor muscular movements without emotion, e.g., extending the legs, walking or turning the body caused an acceleration of from 5 to 20 beats.

The hyperglycemia and glycosuria resulting from emotional excitement in man and animals is probably associated with the discharge of adrenaline, since it has been shown that the continuous rise in blood sugar which occurs during the emotional reactions (sham rage) following removal of the cerebral cortex (p. 884), is dependent upon the adrenals. The blood sugar continues to rise after this operation, though the glycogen stores of the liver are removed from nervous control by sectioning the hepatic nerves. On the other hand, the effect does not occur after removal of the adrenals, even though the hepatic nerves are intact. In those instances in which the emotional state does not follow the operation of decortication, the hyperglycemic effect also fails to appear. Puncture of the floor of the fourth ventricle and stimulation of the adrenal nerves also cause

hyperglycemia though the hepatic nerves have been previously cut.

Though direct evidence is difficult to obtain it is reasonable to assume that besides the effects mentioned above, adrenaline when secreted into the blood stream brings about other actions which we have seen to be characteristic of its action when injected.

A recapitulation of the actions of the sympatho-adrenal system will show how important these several actions are in fitting an animal for defense or flight; for attack or pursuit. (1) The rise in general blood pressure accompanied by dilatation of the vessels of the contracting skeletal muscles, and of the coronary arteries; and the increased force and output of the heart, raise the circulatory system to a state of maximal efficiency. (2) Hyperglycemia indicates the mobilization of the carbohydrate stores of the liver: thus an adequate supply of fuel for the active muscles is ensured; muscular fatigue occurs less readily. (3) Increased oxygen capacity of the blood is brought about by the discharge of red cells from the spleen. (4) Bronchiolar dilatation and an increase in the rate and depth of respiration permit an increased oxygen intake to supply the tissue cells; at the same time the level of oxygen consumption of the latter is raised. (5) Shortened coagulation time of the blood lessens the danger from hemorrhage. (6) Finally, the emotional manifestations of man and the fighting attitudes or defense reactions of various animals are sympatho-adrenal effects, e.g., pupillary dilatation; protrusion of the eyeballs; cutaneous vasoconstriction; acceleration of the heart; contraction of smooth muscle in the skin causing "gooseflesh" in man, and the erection of the hairs, quills or feathers of animals; sweating; salivary secretion (cat),⁴ and the color changes of some cold-blooded animals

The tonus theory of adrenal function

It has been thought in the past that the medullo-adrenal secretion maintained the sympathetic nerve endings in a state of sensitivity or tone and that the height of the normal blood pressure was dependent upon the continuous discharge of the hormone into the blood. Low blood pressure has been ascribed to adrenaline deficiency (so-called hypoadrenalemia) and essential

⁴ It is an interesting and perhaps a significant fact that in the cat in which spitting is a defense reaction sympathetic stimulation causes a profuse watery flow of juice from the salivary glands. In other animals sympathetic stimulation causes a scanty flow of viscid saliva, a watery secretion being caused by parasympathetic excitation.

hypertension to the liberation of adrenaline in excess (hyperadrenalemia). Nevertheless, the experimental evidence against such conjectures is conclusive. In the first place, if one adrenal be excised and the medulla of the other burnt or curetted away, no fall in blood pressure occurs, so long as a portion of the cortex remains. Furthermore, even if any significant quantity of the hormone were in circulation under ordinary resting conditions its concentration would be within the range which would cause a depressor rather than a pressor effect (p. 686). That a continuous pressor effect is not exerted by circulating adrenaline was shown by Hoskins. He injected small quantities of adrenaline into the blood stream of a quiet animal. A fall in pressure resulted, whereas, if the effect of the injected dose had become added to a pressor effect of adrenaline already present in the blood stream it is obvious that a rise in blood pressure should have occurred. Not until the injected dose was considerably increased did any pressor effect appear. To cite other observations against the view that essential hypertension is due to overactivity of the adrenal medulla, the blood of subjects of this condition does not contain an appreciable amount of adrenaline and the glands of such persons do not contain an adrenaline store greater than normal.

There are certain types of vascular hypertension, however, which are most probably, or certainly, of adrenal origin. The high blood pressure of pituitary basophilism, for example (p. 737), is probably the result of adrenal stimulation. Adenoma of the adrenal medulla itself or of outlying chromaffin tissue (phaeochromocytomata) is certainly the cause of hypertension in some instances. The hypertension is paroxysmal in character, due apparently to the periodical discharge of adrenaline into the blood stream; it is not uncommonly accompanied by hyperglycemia.

DENERVATION OF THE ADRENALS IN THE HUMAN SUBJECT

This operation has been performed with the object of influencing the course of certain diseases, e.g., diabetes, exophthalmic goiter, in which hypersecretion of the adrenal medulla has been supposed to play a part in their causation. It cannot be stated too emphatically, however, that attempts to modify adrenal function in this manner are never justified. Rogoff has reported a case of Addison's disease (p. 697) which apparently was the direct result of denervation of the adrenals in a diabetic subject.

SYMPATHIN

It has been mentioned that the *prompt* acceleration of the denervated heart does not occur in adrenalectomized animals during excitement, sensory nerve stimulation, etc. Cannon and his colleagues find, however, that a *slowly developed* acceleration of the denervated heart occurs during

excitement or muscular activity though the adrenals have been extirpated. The increase in heart rate takes about a minute to develop, reaches its maximum in about 3 minutes and then gradually subsides. Its occurrence is not prevented by the removal of all accessory adrenal tissue, by hypophysectomy or by the excision of the thyroid, parathyroids or gonads, or by denervation of the liver. It is abolished, however, by removal of the sympathetic chains. It was also found that the characteristic slow acceleration of the heart occurred when the lower abdominal sympathetic chain was stimulated. The latter nerve contains fibers supplying the smooth muscle of the skin which are responsible for the erection of the tail hairs. Secretion of the denervated salivary glands, contraction of the nictitating membrane, a rise in blood pressure and of blood sugar also resulted from the stimulation of the abdominal sympathetic. These effects as well as the cardiac acceleration occurred though the cord had been divided in the thoracic region, and the sympathetic chain above this level removed. A material originating in the hind part of the animal was evidently conveyed in the blood stream to the heart and other structures mentioned. Blocking the blood flow returning from the area supplied by the stimulated nerve or removal of the patch of skin prevented the cardiac response. As a result of these researches Cannon and his associates conclude that during sympathetic stimulation a chemical substance resembling adrenaline in its action is liberated from the sympathetic endings supplying the smooth muscle of the skin. They have named this substance *sympathin*. Evidence has also been procured for the liberation of sympathin from other sympathetic nerves, e.g., those of the gastrointestinal tract, cardioaccelerators, hepatic nerves, hypogastric, cervical sympathetic, etc.

Sympathin though resembling adrenaline is not, according to Cannon and Rosenblueth, identical with it. Adrenaline, as we have seen, causes both excitatory and inhibitory effects, whereas evidence is presented for the existence of two kinds of sympathin, one purely excitatory, the other purely inhibitory. The former, called *sympathin E*, is liberated within structures excited by sympathetic impulses, e.g., cardiac muscle, liver, vessels and smooth muscle of the skin, etc. The other sympathin, called *sympathin I*, is liberated in structures inhibited by sympathetic impulses, e.g., intestinal wall, coronary vessels, etc.

Though in many ways sympathin and adrenaline resemble one another, e.g., the actions of both augmented by cocaine and both give the Viale reaction, Cannon and Rosenblueth base their view that the two agents are not identical upon certain similarities. For example, adrenaline causes both excitatory and inhibitory effects which cannot be separated, whereas a sympathin with an excitatory action alone can be demonstrated. When a branch of the splanchnic nerve sending fibers to both the cecum and the liver is stimulated, the sympathin produced (by excitatory impulses to blood vessels of the liver, and inhibitory impulses to intestine) contracts the nictitating membrane and relaxes the non-pregnant uterus; but if the nerve fibers to the liver are stimulated alone the sympathin which is released causes contraction of the nictitating membrane but does not inhibit the uterus. The converse experiment, namely, stimulation of nerves with a purely inhibitory action, cannot be performed, for such do not exist, since some constrictor (excitatory) fibers to blood vessels are always present. Another distinction between adrenaline and sympathin is afforded by the action of ergotoxin. Adrenaline administration following treatment with ergotoxine causes a fall in blood pressure, whereas sympathin liberated by the stimulation of the hepatic nerves causes a rise.

THE ADRENAL CORTEX

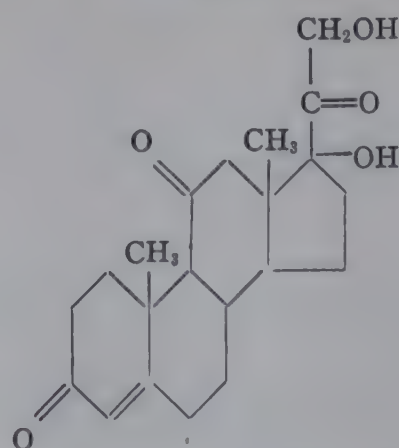
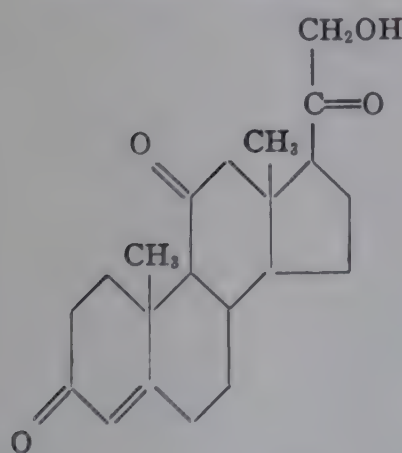
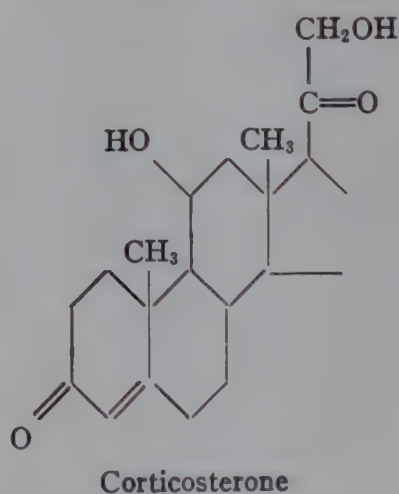
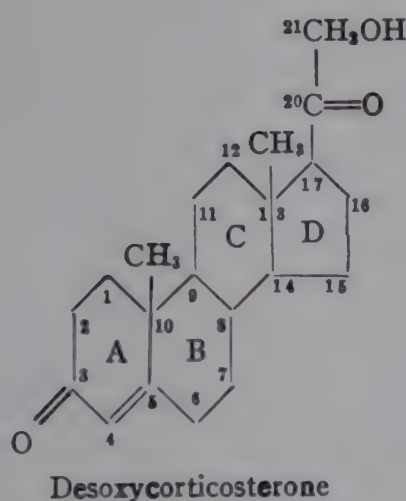
FUNCTIONS

The cortex of the adrenal, unlike the medulla, is essential to life. Removal of more than about five-sixths of this part of the adrenal causes death within a few days. Removal of the intermediate body of Elasmobranch fishes (p. 684) is also fatal. Stewart and Rogoff found that the average survival time of dogs after complete double adrenalectomy was 10 days and the maximal time 15 days. They observed that pregnant animals, those in heat (pseudopregnancy) actually survived much longer. For this reason, they suggested that some substance formed at these times substituted for the cortical hormone. This observation has been amply confirmed, and it has been shown further that the survival of adrenalectomized dogs and rats is extended by the administration of progesterone (p. 752). Stewart and Rogoff showed also that the lives of completely adrenalectomized animals could be prolonged by the injection of a cortical extract combined with transfusion of saline. Hartman too obtained a cortical extract which he called *cortin*. This was capable of definitely prolonging the survival time of adrenalectomized animals. Swingle and Pitts

1930 extracted by means of lipid solvents a very potent substance from the cortex which counteracted the effects of adrenal deprivation. When treated with this preparation adrenalectomized animals survived indefinitely; it also proved highly successful in the treatment of Addison's disease.⁵

A brief outline of the chemistry of adreno-cortical principles. Some twenty crystalline steroid compounds have been isolated from the adrenal cortex which exhibit in greater or less degree the physiological properties of crude cortical extracts. The formulae of four of these, namely, *desoxycorticosterone*, *corticosterone*, *11-dehydrocorticosterone* (Kendall's compound A) and *11-dehydro-17-hydroxycorticosterone* (Kendall's compound "E" and Reichstein's compound "Fa6") are given below.

This synthetic compound, which exerts its action predominantly upon water and salt (Na and K) metabolism, is administered in the form of the acetate either subcutaneously or intramuscularly in oil, or in the form of pellets implanted beneath the skin. A material called the *amorphous fraction* remains after the removal of these crystalline compounds from the crude extract. The several physiological actions obtained with a crude extract are not all exhibited, at least fully, by any one of these compounds. Thus, *desoxycorticosterone* has little or no effect upon carbohydrate metabolism, whereas *corticosterone* which shows this effect to a marked degree exerts a minor action upon the metabolism of water and salt (see also p. 695). Besides these compounds, with actions specific for the adrenal cortex, steroids



Corticosterone was isolated by Reichstein and his associates in 1937. Desoxycorticosterone, which has one less oxygen atom, was synthesized later by Steiger and Reichstein from stigmasterol.

⁵ Dogs are employed in assaying the potency of the extract. A dog unit (D.U.) is defined as the minimal daily quantity per kilo of body weight which will maintain for from 7-10 days an adrenalectomized dog in normal condition, as judged by the blood, non-protein nitrogen level and body weight.

with actions of estrone, progesterone and the male hormone, respectively, have been isolated from the adrenal cortex. The last mentioned principle has been named *adrenosterone*.

The manifestations of cortical deficiency in animals

An animal which has been completely adrenalectomized shows the following features during the short period of its survival. Loss of appetite,

(particularly for fats), vomiting, diarrhea, rapid loss of weight, weakness and prostration; fall in body temperature by several degrees; hypotension; and a reduction of 20 per cent or so in the basal metabolic rate (fig. 271). The stimulus of a cold environment upon heat production is much less than in normal animals. The blood becomes concentrated (loss of plasma water) and shows a fall in sodium and sugar, and a rise in non-protein nitrogen, phosphate, calcium and especially of potassium. There are, reduced excretion of urinary nitrogen and other signs of renal failure. Anemia may occur.⁶ The glycogen stores of the liver and muscles are reduced. These changes, as well as the effect upon the electrolyte concentrations of the blood, are detectable within 42 hours

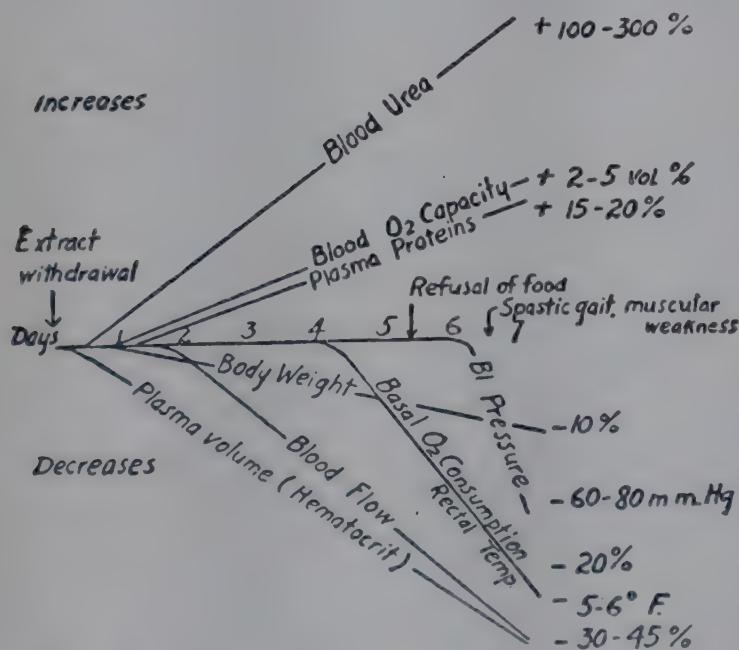


FIG. 271. Characteristic changes in metabolism, circulation and blood concentration in a group of adrenalectomized animals following withdrawal of extract. (After Loeb.)

following adrenalectomy. Post-mortem examination frequently shows congestion of the gastrointestinal tract and pancreas.

The foregoing picture can be entirely prevented by the administration of an extract of the cortex and even comatose animals can be restored to health; heat, pregnancy and lactation proceed normally in adrenalectomized bitches, and growth is maintained in adrenalectomized puppies.

The cortex quite evidently is concerned in some way with mineral and water metabolism. In adrenalectomized animals as well as in the adrenal

⁶ Pigmentation as seen in man has not been observed in lower animals, though, according to Hartman in white cats a grayish discoloration of the skin may be noted. Bronze freckles have also been described in adrenalectomized monkeys and pigmented spots in the buccal mucosa of dogs.

insufficiency of man, a marked reduction in total base occurs which is due entirely to the loss of sodium. The potassium concentration of the serum is raised above the normal level, the rise being due to reduced excretion by the kidney as well as to leakage from the tissue cells into the extracellular fluids. The loss of sodium is accompanied by an increased elimination of water. Marked dehydration results. The administration of sodium chloride to adrenalectomized animals and a reduction in the potassium intake exert a definitely beneficial effect. On the other hand the withdrawal of salt from the diet increases the severity of the condition. The sodium rather than the chloride ion is the important factor.

The reduction of blood sodium was observed originally by Bauman and Kurland, and the beneficial effects of transfusions of saline in sustaining adrenalectomized animals were described by Stewart and Rogoff and by Hartman, but the importance of sodium loss in the development of the symptoms was first pointed out by Loeb and his associates and by Harrop. The value of a low potassium content of the diet in the survival of adrenalectomized animals was shown by Allen and his associates. Completely adrenalectomized animals can be maintained in good health without cortin if placed upon a diet low in potassium but high in sodium chloride and, in order to prevent the acidosis which otherwise develops, containing sodium citrate. The tendency to hypoglycemia is controlled by a high carbohydrate diet. These measures, however, do not completely restore the animal to a physiological state, for they are unable to withstand stress or to perform work with full efficiency.

It is claimed that increased susceptibility to certain toxic agents, e.g., histamine, morphine, diphtheria toxin, etc., is another manifestation of adrenal insufficiency. The adrenal cortex also appears to be concerned in some way with the maintenance of the nutrition of certain nervous tissues; degenerative changes have been noticed in autonomic ganglia (cervical, stellate and celiac) following adrenalectomy, and almost complete loss of function of the vasomotor and cardiac accelerator nerves in adrenalectomized animals was demonstrated years ago by Elliott and more recently by Clegburn and associates. The intestinal absorption of water and electrolytes and the diuretic response to water drinking are greatly reduced in adrenalectomized animals. The relationship of the adrenal cortex to the development of renal hypertension is described on page 132 and its use in burn shock on page 767. The rôle of the cortex in lactation is discussed on page 767.

The physiological actions of the cortical extract and of its different fractions

The general description just given of the actions of the relatively crude extract of the adrenal cortex (cortin) in restoring the health of adrenalectomized animals may now be supplemented by an account of certain other effects which result from the administration of adrenocortical fractions. Cortin, as shown by Britton and his associates, raises the blood sugar and increases the liver glycogen in normal as well as in adrenalectomized animals. The effect upon carbohydrate metabolism is exhibited by those compounds with an oxygen atom at carbon 11, especially corticosterone. Their fundamental action is upon the conversion of protein to glucose (gluconeogenesis), the hyperglycemic effect being accompanied by an increase in the glycogen stores. These compounds thus exert a glycotropic or anti-insulin action and are capable of preventing insulin convulsions. Nothing further need be said here concerning the rôle played by the adrenal cortex in carbohydrate metabolism, since this has been dealt with in Chapter L. The effect of cortin upon the electrolyte concentrations in the body fluids is not confined to adrenalectomized animals, for Thorn and his associates have shown that it reduces the urinary excretion of sodium and increases that of potassium in healthy persons and in normal dogs. Cortin postpones muscular fatigue, a normal animal being capable of greater work under its influence. This action is exhibited to the greatest degree by corticosterone and other compounds possessing an oxygen atom at C_{11} ; desoxycorticosterone is inert in this respect. Corticosterone, dehydrocorticosterone and compound E exert a minimal effect upon water and salt metabolism. The restoration of normal kidney function is exhibited by desoxycorticosterone but to the greatest degree by the amorphous fraction. Either of these compounds causes a prompt reduction in the non-protein nitrogen of the blood. The most outstanding action of desoxycorticosterone is upon salt and water metabolism; it increases the plasma volume and the concentration of sodium in the body fluids, but reduces that of potassium. These effects are due largely but not entirely to an action upon the renal tubules (p. 385). They are partly extrarenal for this steroid appears to influence membrane permeability of the tissues generally; the intracellular potassium concentration is increased and the sodium concentration reduced. As a

result of its effect in causing the retention of sodium and water, desoxycorticosterone administration may be followed by edema. In large doses it may cause more serious effects, e.g., hypertension, dilatation of the right ventricle and pulmonary congestion. Death from cardiac failure has resulted from its clinical use. The manner in which desoxycorticosterone induces these ill-effects is not altogether clear. The rapid increase in plasma volume, and, as a result of this, the extra burden thrown upon the cardiovascular system is suspected of being an important factor. Depression of the potassium concentration of the body fluids may be the lethal factor in some instances; Loeb and his associates have shown that the administration of desoxycorticosterone to animals may lower the potassium level to the point where paralysis results. The administration of potassium salts or a reduction in the sodium intake is undoubtedly of benefit in patients receiving large doses of desoxycorticosterone.

An influence upon growth has been demonstrated (by Hartman and Thorn) for desoxycorticosterone and the amorphous fraction. Young adrenalectomized animals show retarded growth which is resumed when either of these preparations is administered. Corticosterone and compound E, on the contrary, actually inhibit growth.

The reputed action of cortical principles in reducing capillary permeability should be mentioned, since such an effect affords a theoretical basis for their use in surgical and burn shock. Menkin has reported that the dilatation and increased permeability of the capillary vessels caused by inflammatory exudates (see p. 75) can be reduced or prevented by the administration of extracts of the adrenal cortex.

The table on page 696, summarizes the principle physiological actions of the different fractions of the adrenal cortex.

The adrenal cortex and the sex functions. Several observations point to the cortex as being in some way associated functionally with the gonads; among these observations are (a) animals during heat or pregnancy withstand adrenalectomy better than at other times, and progesterone lengthens the life-span of adrenalectomized rats; desoxycorticosterone, on the other hand, exhibits progesterone activity. Estrogens and androgens can be extracted from the adrenal cortex and are found in normal urine. The excretion of these substances also occurs in eunuchs and in ovariectomized women, which indicates that they are

FRACTION OF ADRENAL CORTEX	PRIMARY PHYSIOLOGICAL ACTION
Corticosterone, dehydrocorticosterone and compound E (compounds with oxygen atom at C ₁₁)	<div><div>(a) Gluconeogenesis (leading to hyperglycemia and increase in glycogen stores)</div><div>(b) Postponement of muscular fatigue</div></div>
Desoxycorticosterone	<div><div>(a) Greatest effect upon salt metabolism—retention of sodium and elimination of potassium increase of plasma volume</div><div>(b) Second to amorphous fraction in restoring renal function</div><div>(c) Most effective in maintaining life in adrenalectomized animals</div></div>
Amorphous fraction	<div><div>(a) Most effective in restoring renal function</div><div>(b) Nearly as potent as desoxycorticosterone in maintaining life in adrenalectomized animals</div></div>

Certain other effects of cortical principles, some of which have been referred to elsewhere, may be mentioned very briefly. The administration to normal rats of corticosterone and of other compounds with an oxygen atom at C₁₁ causes atrophy of the adrenal and thymus within a week or ten days. Progesterone activity of desoxycorticosterone has been demonstrated. As already stated (p. 694) sensitivity to certain toxic agents is increased by adrenalectomy; adrenalectomized animals are also less resistant to cold. Cortical extracts correct these defects. Corticosterone, compound E and the amorphous fraction are about equally effective in protecting against low temperatures; desoxycorticosterone is less active. The parenteral administration of the latter compound, especially if combined with the administration of sodium chloride, is effective against the action of histamine and has been reported to be of benefit in the treatment of severe infections. Hartman and his associates have secured evidence of a relationship between cortin and vitamin C. Cortical extracts relatively free from vitamin C are capable, it is stated, of partially protecting animals from vitamin C deficiency.

derived, in part at least, from the adrenal cortex. It is not improbable that normally the adrenal

cortex, through the manufacture and liberation of these hormones plays a rôle in the control of the sex functions. The persistence of the sex libido after the excision of the gonads (p. 744) conform with such an idea. (b) corticosterone and the sex hormones are closely related in chemical structure (c) the cortex enlarges during pregnancy, and special cells (cells of Stilling) appear in the adrenal cortex of the frog during the mating season; (d) the ovaries of hypophysectomized tadpoles are enlarged by injections of cortical extract; (e) in women the intermenstrual periods are said to be shortened by from 3 to 5 days by the administration of cortical extract (Hartman and associates) (f) cortical extracts have been reported to cause precocious sexual maturity in rats; (g) sexual abnormalities are striking features associated with tumors of cortical tissue (p. 698); (h) the origin of the genital organs and cortex from a common embryonic tissue (celomic epithelium).

The immediate cause of death in cortical deficiency has been a much debated question. Concentration of the blood due to the loss of blood fluid through abnormally permeable capillaries is a prominent feature in animals dying of adrenal insufficiency. Swingle and Pfiffner believe that this increased capillary permeability is an important if not the primary factor in causing death and suggest that the hormone in some way maintains normal capillary permeability and a balanced interchange of fluid between the tissue and the vessels. A normal animal reacts to hemorrhage by dilution of the blood and a rapid restoration of the blood volume. In the adrenalectomized animal, on the other hand, hemorrhage fails to cause blood dilution. These workers draw attention to the similarity of the manifestations of adrenal insufficiency and surgical shock (p. 258). Others stress the disturbance in mineral metabolism as the basic lethal factor and state that most of the effects of adrenalectomy can be induced by the intravenous injection of potassium salt. Britton and his associates have shown, however, that adrenalectomy in the opossum does not cause a loss of sodium chloride, which throws some doubt upon this explanation, for if the loss of sodium chloride were of fundamental importance one would not expect a species difference. Furthermore, some subjects of Addison's disease die although the electrolytes of the blood have been restored to normal. In certain instances hyperglycemia is the immediate cause of death.

DISEASE OF THE ADRENAL CORTEX IN MAN

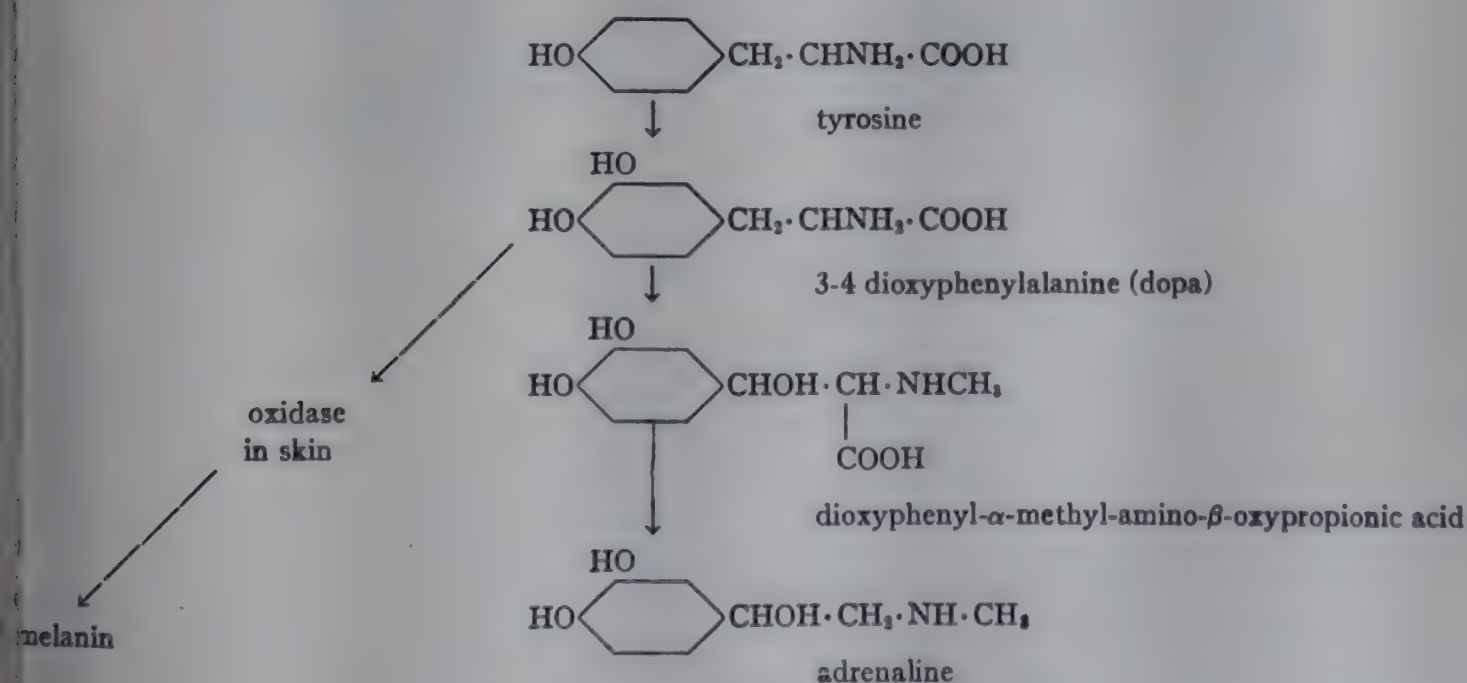
Addison's disease

The syndrome known today as Addison's disease was first described (in 1855) by Thomas Addison and ascribed by him to tuberculous disease of the adrenals. Experimental and clinical observations since that time have fully substantiated Addison's conclusion that the disease is due to adrenal involvement. Tuberculous disease of the gland is found, however, in only a proportion of the cases. It has also been shown that deficiency of the cortex and not of the medulla is the essential cause of the disease. Its chief features, which closely resemble those seen in adrenalectomized animals, are: (a) muscular weakness and languor, (b) low blood pressure and reduced circulation rate, (c) gastro-intestinal disturbances, loss of appetite (anorexia), hypohydria and vomiting, (d) pigmentation of the skin and mucous membranes, bronzing, tanning or a dirty brown cutaneous discoloration being a classical symptom of the disease, (e) lowered metabolic rate, subnormal temperature, sodium loss and a rise in serum potassium, reduced blood volume (plasma loss), dehydration and loss of weight, (f) renal insufficiency with consequent rise in blood nonprotein nitrogen, (g) depression of the sexual functions, (h) hypoglycemia may occur

normal pigmentation is greatest (fig. 272). The palms of the hands and soles of the feet remain pale. The discoloration is due to the excessive accumulation of the normal cutaneous pigment, *melanin*. This is deposited chiefly in the basal cells of the epidermis, but pigment granules are also found in the dermis. The change in pigment metabolism which causes the deposits is unknown.⁷ Szent-Györgyi found that ascorbic acid which, as already mentioned, is present in relatively high concentration in the adrenal cortex inhibits pigment formation in plant tissue but it remains to be shown that a lack of this substance in Addison's disease is responsible in any way for the bronzing.

Addison's disease unless treated with cortical hormone or with a diet of high salt and low

⁷ Bloch found that sections of normal skin became deeply pigmented when placed in a dilute solution of 3:4 dioxypyphenylalanine; albino skin treated similarly remained unpigmented. Solutions of other aromatic compounds (e.g., tyrosine, tryptophane, pyrogallol, etc.) did not cause pigmentation of skin sections. Bloch concluded that *dioxypyphenylalanine*, which he called *dopa*, was the precursor of melanin, the conversion being brought about by an oxidizing enzyme (*dopa oxidase*) in the skin. A theory to account for the excess pigment of Addison's disease has been formulated upon the basis that *dopa* is a likely intermediary in the formation of adrenaline from tyrosine. In deficiency of the cortex it is postulated that a greater amount of *dopa* is converted to melanin and less into adrenaline. Thus



and be the immediate cause of death. The pigmentation may be so deep as to cause the patient to be mistaken for a mulatto; it is most pronounced in those regions, nipples, abdomen, etc., where the

This theory implies that the adrenal cortex is concerned in the production of adrenaline from a precursor. There is no evidence, however, that the cortex possesses this function, and it is even a matter for speculation whether or not *dopa* represents a stage in the formation of adrenaline (see p. 685).

potassium content, is almost invariably fatal within from 1 to 3 years. Unfortunately, the results of treatment are not uniformly good. In some subjects the course of the disease is apparently little altered by treatment. In others, however, remarkable improvement takes place. Patients, even in a collapsed or comatose state, have been brought back to health by administration of the hormone aided by a diet suitably adjusted as to its mineral constituents. The pigmentation fades, often rapidly, the metabolic rate and the blood pressure rise, and the strength returns. As an illustration of the almost specific action of salt in the treatment of Addison's disease the following case reported by Loeb and his associates may be cited. A female patient upon a high salt diet was able to be up and about the

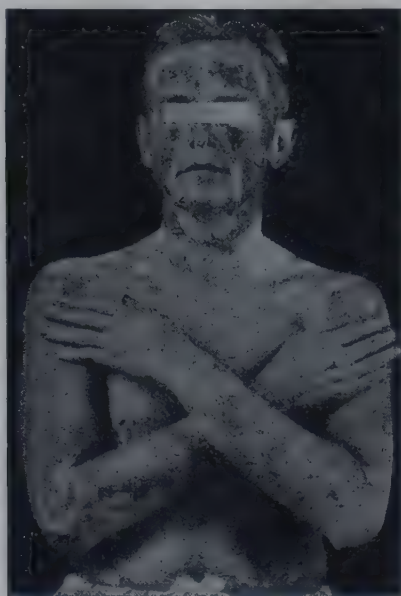


FIG. 272. Showing pigmentation of the skin together with patches of depigmentation in a patient with Addison's disease. (After Loeb.)

ward. When her salt intake was restricted to 2 grams daily she was so weak by the end of the first day that she had to remain in bed; by the next day there were nausea and extreme prostration. Rapid improvement followed when the salt intake was restored to its original level. It follows that in cases in which a diagnosis of Addison's disease is in doubt important assistance will be afforded by noting the effects of a high and a low salt intake, respectively, upon the patient's condition. This in essence is the so-called *provocative test* of Wilder and his associates.

Cortical tumors—adrenogenital syndrome, pseudohermaphroditism

Tumors composed of cortical tissue may arise in the adrenal itself or in aberrant collections of cortical cells (adrenal "rests") which are found

in the broad ligament of the uterus, in the neighborhood of the testes or in the retroperitoneal tissue of the abdomen or pelvis. Such growths may occur in children or in adults, and are associated with extraordinary abnormalities of development especially of the *accessory organs of sex* and of the *secondary sex characters* (p. 743).

When these growths occur in young children puberty appears prematurely; a male child of 4 or 5 years, for example, may show the sexual development of an adult (fig. 273). The testes and penis are enlarged, hair may appear upon the chest, pubis and face, and there may be precocious sexual desire. There may also be unusual muscular development or extreme obesity. Children



FIG. 273. Enlarged abdomen and precocious sexual development of a boy aged thirty months. A mass palpated in the abdomen was probably a suprarenal cortical tumor. (After Rowntree and Ball.)

showing these characters have been described as resembling "an infant Hercules" (Herculean type of Weber), or "a burly brewer's drayman" (Guthrie). Growth is rapid as a rule, but the epiphyses fuse early; young subjects of the disease therefore do not reach full stature.

In little girls the breasts hypertrophy, hair appears on the mons veneris and around the vulva; the uterus develops prematurely, the clitoris hypertrophied and menstruation may occur. In appearance such children resemble stout little women. Adult women who are subjects of the disease become mannish in appearance and disposition (virilism, fig. 274). The voice deepens, menstruation ceases, the breasts atrophy and

hair may grow upon the face, chest and limbs; homosexuality is a common feature. The urinary excretion of androgens is greatly increased. The nature of the effects upon the female sexual processes therefore differs in accordance with the age at which the disease makes its appearance. In some adult female subjects, the virilism is accompanied by glycosuria and decreased sugar tolerance. This type is known as the Achard-Tiers syndrome and was described by these authors as the "diabetes of bearded women." Adult

According to Broster and Vines, many cases of virilism are associated with a diffuse hyperplasia of the adrenal cortex rather than with a definite tumor of cortical tissue. These observers have made the interesting discovery that the hyperplastic or tumor tissue contains large numbers of cells which have an affinity for fuchsin (fuchsinophil cells). Cells possessing this property are normally absent from the mature adrenal or present only in very small numbers. They are a characteristic feature, however, of the fetal adrenal of both sexes between the 10th and 17th weeks (in the case of the male) and between the 11th and 15th weeks



FIG. 274. Virilism due to adrenal tumor. In center, at age of 28 years before the onset of the disease; on right, at age of 35 years at height of disease. (After Lescher.)

female subjects of cortical tumors, as a rule, give no evidence of endocrine disturbances. In some, however, an exaggeration of the masculine characters is manifest, e.g., enlargement of the penis, a tendency to hirsutism and increased sexual appetite. More commonly, a certain degree of feminization is observed, e.g., enlargement of the mammae, atrophy of the testes and a feminine distribution of fat. In some cases of cortical tumor the clinical picture closely resembles that of pituitary basophilism (p. 737).

(in the case of the female) but disappear thereafter. These observers suggest that virilism is due to the elaboration of a masculinizing hormone by the fuchsinophil cells, and that the female fetus normally passes through a male phase.

Surgical removal of a tumor of cortical tissue may be followed by acute adrenal insufficiency. Such a phenomenon is analogous to the hypocalcemia which follows removal of a parathyroid tumor (p. 709) and illustrates the general principle, which is also exemplified in some cases of thyroid adenoma, that the secretion of a normal endocrine organ is inhibited by that derived from another source (e.g., neoplasm or injection).

CHAPTER LX

THE PARATHYROID GLANDS AND CALCIUM METABOLISM

THE PARATHYROIDS

Development and structure

These glands were first recognized as separate structures and described by Sandstrom (1880). He gave them their present name in the belief that they were remnants of embryonic thyroid tissue. They arise, however, quite independently of the thyroid from the entodermic lining of the III and IV visceral clefts in close association with the origin of the thymus. Nor have they any known functional relationship with the thyroid. The parathyroids are usually stated to be four in number, two in relation to the dorsal surface of each thyroid lobe. The upper one on each side is called the "external" or "parathyroid IV." It lies near the upper pole of the thyroid and is often embedded in the latter's substance. The lower one—the "internal" or "parathyroid III"—is situated near the lower pole of the thyroid or at a variable distance below this level. It is drawn into a position below (caudal to) parathyroid IV in early embryonic life. The number of parathyroids and their positions are, however, very inconstant, in man as well as in animals, and accessory parathyroid tissue may be found anywhere in the neck or even in the thorax embedded within the thymus. The Roman numerals III and IV refer to the gill-cleft from which the gland arose. The terms "internal" or "external" signify the proximity of the gland to the mesial or to the lateral aspect, respectively, of the thyroid lobe. The human parathyroids are roughly oval in shape, and about 6 mm. in length.

The parathyroid tissue is composed of large round cells, closely packed into masses separated by capillary sinuses; the cells show no alveolar arrangement; in the adult gland they are of two main types. (a) *Clear chief cells*. These have large nuclei; the protoplasm stains poorly and is usually non-granular. These cells are, apparently, the essential secreting cells of the gland, since they are the only ones present in the human gland up to the 10th year, and at any age in some animals, e.g., the dog. (b) *Oxyphil cells*. These are larger than the preceding and contain granules in their cytoplasm which stain with eosin. They do not appear in the human gland until after the 10th year and are entirely absent from the glands of the dog.

The *blood supply* is very rich and derived from branches of the *inferior thyroid artery*. The *nerve supply* is scanty and the fibers are probably entirely vasomotor in character. They have the same origin as those innervating the thyroid. Secretory nerves have not been demonstrated. The functional activity of the parathyroids is possibly controlled by a hormone liberated by the anterior lobe of the pituitary (p. 728).

THE EFFECTS OF PARATHYROIDECTOMY— HYOPARATHYROIDISM

The small size of the parathyroids in laboratory animals and the fact that they are often embedded in the thyroid make their separate removal by operation very difficult if not impossible. The usual experimental procedure is to remove the thyroid. When this is carried out upon cats or dogs a sufficient proportion of parathyroid tissue is usually removed along with the thyroid to produce urgent symptoms of parathyroid deficiency. These symptoms constitute the condition known as *tetany*. Since tetany may be produced in other ways (see below) the condition when induced by parathyroid removal is called *parathyroid tetany* or *tetania parathyreopriva*. Tetanic symptoms do not, however, invariably result from complete thyroidectomy. The failure of symptoms to appear is due most likely to the presence of accessory parathyroid tissue, or to one or more of the four glands having been left behind, since it is not unusual for a parathyroid, especially one of the lower pair, to be situated a short distance from the thyroid. A description of the tetanic state is given on p. 702.

In general, young animals are more susceptible to the effects of parathyroid deprivation than older ones. A meat diet also appears to increase the susceptibility. But apart from the factors of age and diet the severity of the tetanic manifestations and the time of their appearance after thyroparathyroidectomy vary greatly in different species and between different individuals of the same species. This variability is also in many cases due to differences in the amount of accessory tissue which exists or to the inconstancy in the position of the glands. In the rabbit, for example, the internal (lower) parathyroids usually lie below the thyroid and unless these are sought for and removed tetany does not, as a rule, develop. Tetany is induced in the rabbit with difficulty by thyroparathyroidectomy, yet the condition can be readily induced by other means (p. 702). In cattle also this operation is not followed by tetany.

In the human subject tetany sometimes follows thyroidectomy for goiter, or for malignant disease, and is then due to the inadvertent or unavoidable

removal of the parathyroids (*post-operative tetany*).¹ The removal of a parathyroid tumor is also frequently followed by tetany (p. 708). Some of the earliest reports of tetany following thyroidectomy came from the surgical clinics of Kocher at Berne, and Reverdin at Geneva. The tetanic symptoms were then ascribed to infection of the operation wound (Kocher) or to thyroid deficiency (Reverdin). Though the parathyroids had been described only a few years previously by Sandstrom, their functions were unknown until the experiments of the French physiologist Gley who

rarely, in adults as a result of defective parathyroid function. Tetany arising in this way does not differ essentially from that following parathyroidectomy. The tetany of infants is usually, however, an accompaniment of rickets and, so far as is known, is then not due to parathyroid deficiency. During the active stage of rickets the serum calcium is little if at all depressed, but during the healing stage of the disease calcium is diverted to the bones and the calcium of the serum falls. It is at this time that tetany occurs (p. 703). Tetany may also be produced in rachitic rats by

TABLE 68*
Types of tetany

	CALCIUM	BICARBONATE OF BLOOD	CHLORINE	pH	PHOSPHORUS
Infantile or idiopathic tetany.....	Reduced	Normal	Normal	Normal	Normal or reduced
Tetany of osteomalacia.....	Reduced	Normal		Normal	Normal or reduced
Tetanies of sprue and celiac rickets.....	Reduced	Normal			
Gastric tetany.....	Normal	Increased	Reduced	Increased	Increased
Bicarbonate tetany.....	Normal	Increased	Reduced	Increased	
Hyperpneic tetany.....	Normal	Increased		Increased	
Parathyroid tetany:					
(a) Experimental.....	Reduced	Normal		Normal	Increased
(b) Post-operative.....	Reduced	Normal			
Phosphate tetany (Na ₂ HPO ₄).....	Reduced	Normal	Normal or increased	Normal or increased	Increased
Citrate tetany.....	Reduced	—	—	—	—
Tetany due to calcium and vitamin D deficiency	Reduced	—	—	—	—
Tetany due to magnesium deficiency.....	Normal	—	—	—	—
Guanidin tetany.....	Normal or slightly reduced	—	—	—	Increased

* With modifications and additions from MacCallum.

in 1892, established the fact that their removal was the cause of the tetanic seizures which followed operations for goiter.

OTHER FORMS OF TETANY

These with the chief changes in blood chemistry are shown in table 68.

Infantile and idiopathic tetany

Tetany occasionally arises spontaneously in infants and may then be due to parathyroid deficiency. Spontaneous, or idiopathic tetany as it is sometimes called occurs also, though

¹ It is not very unusual for mild symptoms of tetany to occur after operation but to disappear later. These are probably due to injury and a temporary functional derangement of parathyroid function.

placing them upon an antirachitic diet (Hess and associates).

The tetanies of osteomalacia and sprue

Osteomalacia is a disease of the bones of adults (p. 656). Its pathogenesis is essentially the same as that of rickets. The serum calcium is often very low; tetany is of common occurrence. Tetany occurs in *celiac rickets and non-tropical sprue* (see p. 657). In the latter disease the absorption of fat and of calcium is defective and the serum calcium depressed. Tetany also sometimes occurs in tropical sprue.

Tetany associated with alkalosis (gastric, hyperpneic, and bicarbonate tetany)

In pyloric obstruction, dilatation of the stomach, or as a result of persistent vomiting from other

causes, the loss of chlorine in the vomitus causes a change in the acid-base balance toward the alkaline side. Tetany follows. Alkalosis is also the apparent cause of the tetany which results from increased pulmonary ventilation. In this case it is the excessive elimination of carbon dioxide which is the cause of the increased blood alkalinity. Collip has suggested that the muscular "cramps" which occur while swimming may be due to the hyperpnea induced by the cold water. Alkalosis is also evidently the cause of the tetany-like seizures which sometimes follow the administration of large quantities of sodium bicarbonate for therapeutic purposes (see also p. 704).

Phosphate tetany

Phosphate tetany is produced experimentally. The intravenous injection of 0.5 gram per kilogram of either the acid or the alkaline sodium (or potassium) phosphate into animals causes a profound and rapid fall in the serum calcium. In dogs, it is only after the injection of the alkaline salts, however, that tetany occurs.² This difference is probably due to the different effects of the two salts upon the acid-base balance—the one tending to cause alkalosis and a reduction in the ionization of calcium, the other acidosis and a relative increase in the concentration of calcium ions (see below). The injection of a neutral mixture of the two salts or of phosphoric acid itself does not cause tetany.

Citrate tetany

An intravenous injection of sodium citrate is a less sure way to induce tetany, but in a certain proportion of animals typical convulsions follow within 15 or 20 minutes after the injection. The serum calcium is lowered.

Tetany due to calcium and vitamin D deficiency

After a period of from 3 to 7 weeks on a diet lacking in calcium, the serum calcium of rats falls to a low level but tetany does not develop unless the diet is also devoid of vitamin D. Even when both calcium and vitamin D are absent from the diet, tetany does not appear spontaneously, but typical convulsive seizures can be induced by stimulation with the galvanic current or by a sudden sound.

MILK FEVER. Hypocalcemia and tetany sometimes occur in cows after calving as a result of the loss of calcium in the milk. The condition is treated by inflating the udder with air, which suppresses milk secretion and causes a rise in the serum calcium, or by

the intravenous injection of calcium. A similar condition is seen in sheep after lambing and is then referred to as "lambing sickness" or "ewe distemper."

Magnesium-deficiency tetany

The general features of this type of tetany are indistinguishable from those due to calcium deficiency. It has been produced in rats, dogs, and young cattle on feeding diets deficient in magnesium. Calves reared upon the whole milk, which has a low magnesium content (0.01 per cent), frequently show severe tetany and may die in convulsions. The blood calcium and phosphorus are within normal limits but the magnesium is reduced to little more than half the normal value. This type of tetany is not known to occur in the human subject.

A GENERAL DESCRIPTION OF THE TETANIC STATE

A. In animals the tetany following parathyroid extirpation has been studied most extensively. Its chief features are: (a) *fall in serum calcium* from the normal level of from 10 to 12 mg. p. 100 cc. to 6 mg. or less. The fall may be very abrupt, reaching the latter value in twenty-four hours, or may be delayed for from forty-eight to seventy-two hours or so. (b) *Rise in inorganic phosphorus of the plasma* from a normal of around 5 mg. per cent to between 6 and 8 mg. or more. (c) *The urinary excretion of calcium and phosphorus is reduced.* (d) *Rapid noisy breathing*³ (100 or more per minute), *high temperature* (104° to 105°F) and *tachycardia*. (e) *Salivation*, often with frothing at the mouth. (f) *Fibrillary twitching of the muscles* followed by *tonic or clonic (jerking) muscular contractions*. The jaws are clenched and the limbs are either stiffly extended or jerked violently; the head is dorsi-flexed. Sometimes there are automatic swimming-like movements of the fore-limbs in dogs, or, in cats, rhythmic jerking movements of the paws, as though the animal were trying to shake water or some other material from them. (g) The muscles show *increased excitability* to the galvanic current (p. 703) and to mechanical stimulation. Normally 6 milliamperes are required to produce cathodal opening contraction (C. O. C.) when the electrode is applied to the skin over the muscle and its nerve. In the tetanic state less than 1 milliampere may be sufficient. The time constant of accommodation is increased (see p. 783). (h) It has been shown by Imrie and Jenkinson that the *phosphocreatine* of the muscles is reduced and

² In rats, according to the results of the experiments of Greenberg and his colleagues, tetany follows the intravenous injection of the di-sodium salt.

³ The increased pulmonary ventilation, by blowing off carbon dioxide and producing a condition of alkalosis, no doubt increases the severity of the symptoms (see tetany of hyperpnea).

rate of resynthesis slower than normal. (h) *Death usually occurs from asphyxia*, due to spasm of the laryngeal and thoracic muscles.

The tetanic symptoms are closely related to the serum calcium level. As this becomes lowered the symptoms, mild at first (perhaps merely slight stiffness of the hind-limbs), become gradually more severe and when the serum calcium has fallen to between 5 and 6 mg. per cent, the tetanic state is usually fully developed.

Parathyroidectomized rats show an increased appetite for calcium; when given a choice between a calcium solution and water they drink more of the former than do normal rats under the same circumstances. As compared with normal animals they drink less of a phosphate solution.

B. In man. In adults, tetany is most frequently due to parathyroid deficiency—the result of an operation for goiter or for the removal of a parathyroid tumor (p. 708). The symptoms are usually less intense than those seen in parathyroidectomized animals, the condition, as a rule, running a more chronic course. Rapid respirations and high temperature are not common features. The serum calcium does not, as a rule, fall below 7 or 8 mg. per cent. Neuromuscular hyperexcitability is the outstanding feature. Though jerking movements or generalized convulsions may occur in children they are unusual in adults. The hypertonic state of the muscles causes the hands and feet to be drawn into typical attitudes which are spoken of as *carpo-pedal spasm* (fig. 275). The hands are flexed at the wrists, and the fingers flexed at the metacarpo-phalangeal but extended at the interphalangeal joints. The thumb is adducted into the palm. This position constitutes the so-called *accoucheur's hand* of tetany. The feet are extended at the ankles and the toes plantarflexed. Spasms of the eye-muscles may be seen, and occasionally spasmodic retention of urine occurs. In infantile tetany spasm of the muscles of the glottis is not uncommon, causing inspiratory stridor (*laryngismus stridulus*). When severe, the laryngeal spasm causes complete closure of the glottis for a time; cyanosis results and when asphyxiation seems imminent a sharp inspiration occurs accompanied by a high-pitched "crowing" sound. These various forms of muscular spasm are grouped under the general term *spasmophilia*.

Latent tetany

Frequently the serum calcium remains just above the critical level at which definite tetanic

symptoms appear. Emotion, some undue strain upon the organism, e.g., pregnancy, lactation or a failure in general health, may, however, precipitate an attack of manifest tetany in a subject who had been suffering from the disease in latent form. Certain tests are employed to uncover this incipient form of the disease: (a) *Chvostek's sign*,—tapping over the facial nerve in front of the ear causes



FIG. 275. Tetany. Description in text. (Upper photograph after Purvis Stewart; lower, after Cabot.)

twitching or spasm of the facial muscles. (b) *Trousseau's sign*,—obstruction of the circulation in the arm by means of blood-pressure armlet causes the hand to assume the typical attitude. The effect is probably due to the anoxemia induced in the muscles of the hand and forearm. (c) *Erb's sign*,—increased excitability of the muscles to the galvanic current already referred to.

PATHOGENESIS OF TETANY

MacCallum and Voetglin discovered that the serum calcium was invariably depressed in tetania parathyreopriva and that the condition was immediately relieved by the intravenous injection of calcium.

With the general recognition of these facts the *calcium deficiency theory* came into being. The low serum calcium found in other forms of tetany, of tetany produced otherwise than through parathyroid deficiency, e.g., the tetanies of rickets, osteomalacia and sprue, also indicates that calcium deficiency is the direct cause of the neuro-muscular hyperexcitability in these conditions. Depression of the serum calcium also explains the convulsions following the injection of phosphate. It is generally accepted that the determining factor in the production of tetany is the concentration of *ionized* calcium (p. 710) in the plasma and extracellular fluids of the body, rather than the *total* calcium concentration. For example, in nephritis with a low serum protein, the total calcium of the serum may be reduced to 3 or 4 mg. per cent, yet tetany does not occur, presumably because the concentration of ionic calcium has not been reduced to the critical level. As shown by the experiments of Loeb upon frog muscle the sodium and potassium ions tend to increase neuromuscular excitability, the calcium and magnesium ions to depress it. The calcium concentration of the tissues themselves (muscle or brain) is not altered in tetany, the increased neuromuscular excitability would therefore appear to be due to an imbalance between the concentration of ionic calcium in the extracellular fluids and within the tissue cells. (See also p. 706.)

It is difficult to assess the importance of hyperphosphatemia as a factor in the production of tetany, for a reciprocal relationship exists in the blood between the concentrations of calcium and phosphorus. Phosphate retention or phosphate injection causes a fall in the calcium of the serum; a rise in the concentration of the calcium of the serum, on the other hand, tends to depress the blood inorganic phosphorus. Nevertheless, tetany can result from a reduction in the serum calcium as in infantile rickets and osteomalacia with a normal concentration of blood phosphate. Hyperphosphatemia, therefore, though undoubtedly increasing the severity of the tetanic symptoms does not appear to play the primary rôle in their development.

The tetany of alkalosis is not easy to explain

upon the basis of calcium deficiency, since in this type the serum calcium is not significantly lowered. It is suggested, however, that the shift of the acid-base balance of the blood toward the alkaline side causes a reduction in the ionic calcium fraction without altering the concentration of the total calcium of the serum. The following equation illustrates the possible relationship between the concentrations of calcium, bicarbonate, phosphate and hydrogen ions.

$$\frac{[\text{Ca}^{++}] [\text{HCO}_3^-] [\text{HPO}_4]}{[\text{H}^+]} = K$$

According to this equation an increase in the concentration of the bicarbonate ions or of phosphate ions or a fall in the concentration of hydrogen ions would cause a reduction in the concentration of ionized calcium without a change in the total calcium level of the serum.

This conception has not been fully tested in direct experiment owing to the lack of a convenient and reliable method for determining the ionic calcium fraction of the serum (p. 710). Certain observations, however, are in conformity with such a hypothesis. The beneficial effect upon tetany of the administration of an acidifying salt such as ammonium chloride, since it is not accompanied by a rise in the total calcium of the serum, and the difference, already mentioned between the actions of the alkaline and acid phosphates (p. 702), may be explained upon such a basis.

It should be borne in mind, however, that the condition known as tetany is simply the manifestation of neuromuscular excitability. It is conceivable that abnormal conditions other than calcium deficiency may alter the excitability of the cells. In other words it need not be assumed that all forms of tetany are due to a common cause.

The question of the neuromuscular mechanism responsible for the tetanic seizures has not received a decisive answer. D. N. Paton and his associates sectioned the cord in parathyroidectomized dogs and observed cessation of the clonic and tonic spasms, but the tremors and the fibrillary twitchings were abolished only by section of the peripheral nerves. The results indicated that the tonic and clonic spasms were supraspinal in origin while the finer movements were dependent upon spinal centers. West more recently concluded that the supraspinal centers were not involved since the characteristic tonic and clonic spasms persisted after section of the cord in the upper thoracic region. The integrity of the spinal reflex arc was

however, considered to be essential for the tonic and clonic manifestations since they were abolished after section of the dorsal roots. The fibrillary movements and the increase electrical excitability of the muscles thus appeared to be dependent upon a peripheral mechanism. They persisted for at least 24 hours after section of both afferent and efferent nerves. In contradiction of West's conclusions, Greenberg and his colleagues state that in rats, tetanic movements of the hind limbs but not of the forelimbs are abolished by transection of the cord at the level of the 7th spinal segment. They conclude that activity of nervous centers above the spinal level is essential for the development of both the tonic and clonic seizures.

TREATMENT OF TETANY

Though the tetanic symptoms are rapidly abolished by the intravenous administration of calcium salts, the beneficial effect is of short duration. Calcium by mouth is of little value in acute tetany, but is of some value in the more chronic forms. Acidifying salts, e.g., ammonium chloride are also of benefit. A single injection of parathyroid extract will relieve the condition in a few hours and hold it in abeyance for several days. In chronic tetany (e.g., post-operative) irradiated ergosterol in the form of dihydrotachysterol or calciferol is of great value, especially when combined with a high calcium and a low phosphorus intake. According to Anderson and Lyall adjustment of the calcium and phosphorus of the diet (0.5 to 0.65 gm. of phosphorus, daily) is capable alone of controlling the symptoms.

THE ACTIONS OF PARATHYROID EXTRACT

The belief in the calcium-regulating function of the parathyroids, which followed naturally upon the discovery that hypocalcemia was an accompaniment of parathyroid deficiency, received spectacular confirmation in 1925. In this year Collip obtained an extract from beef parathyroids which possessed a powerfully hypercalcemic effect.⁴ By the intravenous or subcutaneous

⁴The extract was obtained by boiling fresh glands for 1 hour with 5 per cent HCl. The resulting liquid after cooling was made alkaline to pH 8 by the addition of NaOH. Hydrochloric acid was then added slowly until a maximal isoelectric precipitation of protein occurred. The precipitate was removed by filtration or centrifuging. The filtrate or supernatant fluid contains the active principle. The potency of the extract was assayed upon dogs, a unit being defined as $\frac{1}{100}$ th of the quantity of extract which will cause a rise of 5 mg. per cent in the serum calcium of a 20 kilogram dog within a period of 15 hours. The extract, for which the name "parathormone" was suggested by Collip, is usually sold in 5 cc. vials and has a potency of 20

administration of this extract to parathyroidectomized dogs the serum calcium can be maintained at the normal level. Violent tetanic symptoms are abolished within three or four hours after the injection of 10 or 20 units, and by the daily administration of considerably smaller doses than this the animal is maintained in good health indefinitely. If after the calcium has been raised to normal the administration of the hormone is continued in frequently repeated doses (10 to 20 units twice daily or oftener) or if given in such dosage to a normal animal, overdosage effects are produced. These are, (a) *Early changes in blood chemistry*. The serum calcium rises abruptly and within from twenty-four to forty-eight hours usually reaches a concentration of from 18 to 22 mg. per 100 cc. (fig. 276). During this time the inorganic phosphorus shows a moderate fall followed by a return to normal and a small rise. There is a slight rise in the potassium and magnesium of the serum. (b) *Early symptoms*. During the rise in serum calcium there are loss of appetite, depression and weakness, polyuria, vomiting, diarrhea and dehydration. (c) *The urinary excretion of calcium and phosphorus* is greatly increased. The increased excretion of phosphorus precedes the rise in serum calcium and the increase in urinary calcium. There is little change in the fecal excretion of these elements. (d) *Late blood changes* are; a reduction in the hypercalcemia by 2 or 3 mg. per cent; a pronounced rise in the plasma inorganic phosphorus; a four-fold increase in blood nonprotein nitrogen; a reduction in blood volume by 15 per cent due to plasma loss and, in consequence, concentration of the blood and, a great increase in its viscosity. (e) *Late symptoms*. At the time that these blood changes are occurring urgent symptoms appear,—vomiting of bloody fluid and sometimes the passage of blood-stained stools; signs of renal failure; great prostration ending in death. (f) *At autopsy* the gastro-intestinal mucosa is found to be the seat of extensive hemorrhages, and the stomach and upper part of the intestinal canal contain a quantity of bloody fluid.

The preceding description applies chiefly to dogs. The serum calcium of herbivorous animals, rats, mice, rabbits and guinea pigs, responds much less readily to the extract and the post-mortem picture so characteristic of its effects in dogs and cats, is not seen. In herbivorous animals, on the units per cc. It is effective by intravenous or subcutaneous injection, but is practically inert when given by mouth.

other hand, repeated doses cause the deposit of calcium in the soft tissue (metastatic calcification), particularly of the arterial tree; this is infrequent in dogs. In the human subject hypercalcemia is produced about as easily as it is in dogs. In both man and dogs tolerance to the hormone not infrequently becomes established after a certain number of doses.

The excess calcium in the serum following parathormone overdosage is derived from the skeleton. Bauer, Aub and Albright have shown that repeated doses of the extract to rabbits causes a reduction of the trabeculae of the epiphyses indicating that they serve as a store of calcium, which is rapidly mobilized by the hormone (fig. 277). By the administration of parathormone over long periods a condition corresponding to

level in the blood was conceived to depend upon "series of interlocked equilibria between this compound and inorganic calcium ions." Increase in the concentration of the organic compound in the blood caused corresponding increase in ionic calcium which was furnished by the bones (see also p. 713). After parathyroidectomy conditions were reversed, a fall in concentration of the compound and reduction in ionic calcium resulted. Another view (Greenwald) was that the hormone itself, or a substance formed through its action, increased the solvent power of the plasma for calcium. This substance, designated X, was supposed to unite with calcium ions to form an undissociated organic calcium compound which was stated to resemble calcium citrate. By this action the concentration of calcium ions in the plasma was reduced and the concentration of undissociated calcium increased. Since the plasma was believed to be in equilibrium with solid tricalcium phosphate ($\text{Ca}_3(\text{PO}_4)_2$) of osseous tissue, a reduction in the calcium ion concentration of the

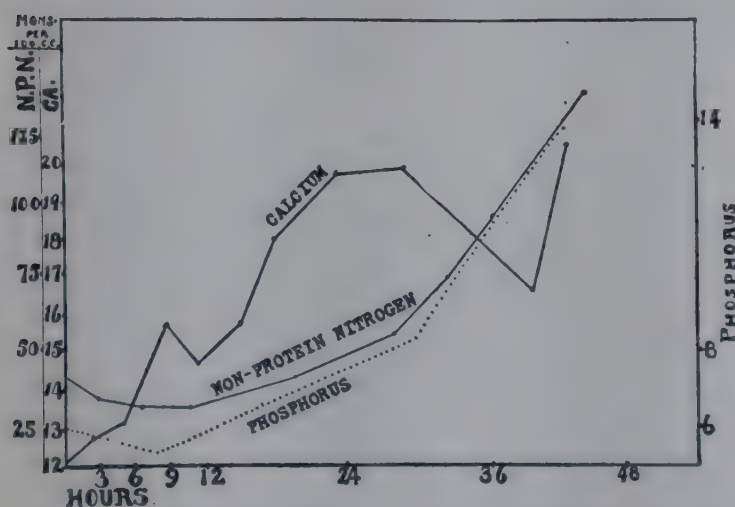


FIG. 276. Curves of serum calcium, blood phosphorus and non-protein nitrogen reproduced from Collip's article describing the effects of parathyroid extract. The curve representing the non-protein nitrogen is not from the same animal as are the curves of serum calcium and blood phosphorus.

osteitis fibrosa cystica of man (see below) has been produced by Bodansky and Jaffe in guinea pigs and by others in rats and puppies. Continued administration of the hormone to experimental animals results in gross and microscopical changes in the glands themselves; they become much reduced in size and their cells appear shrunken, show hydropic degeneration and a diminution in the number of mitotic figures. Such changes suggest that the administered hormone has depressed the functional activity of the glands.

The fundamental nature of the hormone's action has been subject of a considerable amount of discussion and no certain conclusion can be drawn. It has been thought by some (Cameron and Moorhouse) that the hormone controlled the formation of a specific non-diffusible organic calcium compound. The calcium

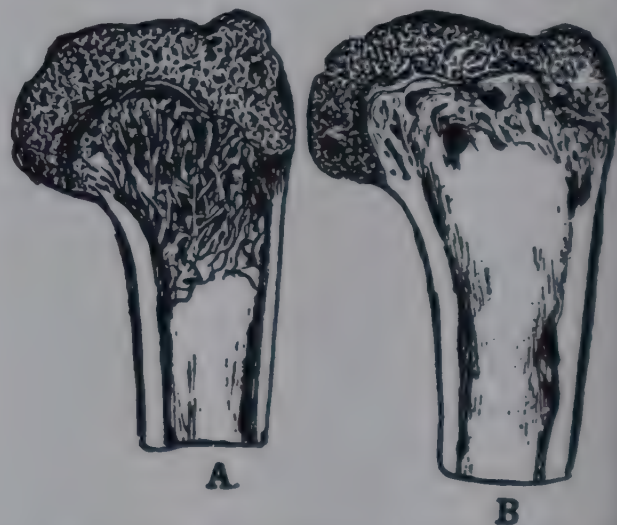


FIG. 277. Showing trabeculae of humeri of cat on (A) a high calcium diet, and (B) on a low calcium diet (Redrawn from Bauer, Aub and Albright.)

plasma resulted in the liberation of calcium ions from the bones. The result was a rise in the total calcium (dissociated plus non-dissociated) of the plasma. Little direct experimental evidence can be cited in support of either of the foregoing views. They picture the liberation of calcium from the bones as a physicochemical process. The histological studies of Selye and rats, on the other hand, suggest that the calcium mobilized by cellular activity. During the hypercalcemia the bony trabeculae showed large numbers of osteoclasts which are believed to be responsible for the removal of calcium. When the animal became tolerant to the hormone the osteoclasts were replaced by osteoblasts and the bone density increased, i.e., calcium was deposited. Schour and Ham, nevertheless, consider the appearance of osteoclasts to be the result of the resorption of calcium from the bone rather than that these elements are active agents. They point out that parathyroid administration interferes with calcification of the dentine of the incisors of rats though osteoclasts are absent.

Aub and his associates believe that the parathyroid hormone exerts its primary action upon phosphorus metabolism, the effects upon the metabolism of calcium being secondary to the depression of the inorganic phosphorus of the blood. Ellsworth suggests that the essential action of the hormone is to lower the renal threshold for phosphate, presumably by inhibiting reabsorption of the latter. The sequence of events, according to these views, are increased excretion of phosphorus, reduced inorganic phosphorus of the blood and a reciprocal rise in serum calcium. An observation which has some bearing upon this subject is the reported failure of the hormone to induce hypercalcemia in bilaterally nephrectomized animals. But the phosphate retention and the hyperphosphatemia which result from this operation might be expected to reduce or even prevent the hypercalcemic effect of the hormone, though the latter had no specific effect upon phosphorus metabolism. However, the important part played by the parathyroid hormone upon phosphorus metabolism cannot be doubted; but such action is probably separate from that upon the metabolism of calcium, for it is possible under certain circumstances to induce hypercalcemia by means of the hormone without causing a corresponding reduction in inorganic phosphorus (Thomson and Pugsley) and *vice versa*.

The liberation of the parathyroid hormone appears to be independent of nervous control. There is suggestive but no definite evidence that the output of the hormone is regulated by the anterior lobe of the pituitary through a parathyrotropic hormone (p. 726). A low level of serum calcium stimulates the liberation of the hormone by the glands, for when the thyroid-parathyroid apparatus was perfused with de-calcified blood and the perfusate injected intravenously into normal dogs, their serum calcium was raised from 1.3 to 4.9 per cent within 3 hours or less (Patt and Luckhardt).

Therapeutic uses of parathyroid extract

In *post-operative tetany* parathormone is of the greatest value in relieving urgent symptoms. It should be combined with large doses of calcium (40 to 60 grains daily of the chloride or larger doses of the lactate or gluconate) and with foods possessing a high calcium content, e.g., milk. Parathormone is generally considered unsuitable for prolonged administration, since it depletes the bones. Also, after a time, tolerance to its action frequently occurs. It would seem, however, to be a logical procedure to give the hormone in doses that would be just sufficient to replace the natural hormone which is lacking, together with large doses of calcium. Calcium chloride, since it supplies calcium directly and through its

acidifying action increases the ionic calcium is of great value. It may be combined with irradiated ergosterol.

In *lead poisoning* the metal is deposited in the bones as tertiary lead phosphate ($Pb_3(PO_4)_2$) displacing calcium from tricalcium phosphate ($Ca_3(PO_4)_2$). Parathormone mobilizes the lead from the bones and increases its excretion in the urine. Ammonium chloride and other acidifying agents have a similar effect. These salts are administered combined with a low calcium diet, which also encourages the mobilization of lead. According to Aub and his associates the increase in hydrogen ion concentration acts by converting the insoluble tertiary lead phosphate into the soluble di-lead salt. Caution should be exercised in the use of de-leading agents since serious effects may result from the sudden entrance of large quantities of the metal into the circulation. Toxic effects due to this cause are combated by a high calcium diet, which favors retention in the bones of the lead compound. When it is considered that the deposition in the bones of ingested lead is a device which protects the body from the toxic effects of the metal it is questionable whether it is desirable, as a rule, to employ de-leading agents. To remove the source of poisoning and permit the metal to be liberated spontaneously and gradually from the skeleton should be sufficient.

It has also been shown that radium deposits in bone may be liberated by parathormone and a low calcium diet.

Attempts to remove extra-skeletal deposits of calcium by means of parathormone have not met with success. This is not unexpected since the action of the hormone in mobilizing calcium and phosphorus is confined to the skeleton and may actually induce calcification of soft tissues (see p. 719).

There is a suggestion that *quite small doses* of parathormone may through the stimulation of osteoblasts encourage calcification, and thus may be of value in the treatment of delayed union of fractures.

THE RELATION OF VITAMIN D TO PARATHYROID FUNCTION

A number of observations suggest a relationship between the actions of *excessive dosage* of vitamin D and the parathyroids. The former, like parathormone, causes a high degree of hypercalcemia, and Hess, Weinstock and Rivkin found that in monkeys hypercalcemia is less readily induced by irradiated ergosterol after parathyroidectomy. Higgins and Sheard found that the parathyroids of chicks deprived of ultraviolet light became hyperplastic, but were restored to normal appearance by the administration of cod-liver oil. Taylor, Weld, Branion and Kay found that the toxic overdosage effects of irradiated ergosterol

were less severe than usual in dogs in which an operation for the complete removal of the parathyroid tissue of the neck had been performed. They also showed that the overdosage effects of parathormone and of irradiated ergosterol were similar. Both substances cause the same degree of hypercalcemia (fig. 278) and hyperphosphatemia, and a rise in the non-protein nitrogen of the blood. In large doses either causes the withdrawal of calcium from the bones and increases the excretion of calcium and phosphorus in the urine. The symptoms during life and the post-mortem findings after poisoning with either material are also identical, and those species (herbivora) resistant to parathormone are simi-

according to some observers increases the absorption of calcium from the intestine; parathormone exerts no such effect.

HYPERPARATHYROIDISM IN MAN. GENERALLY OSTEITIS FIBROSA CYSTICA

This is a condition of the bones which was described some years ago by von Recklinghausen. Though others had previously described this condition it is very often spoken of as von Recklinghausen's disease. The morbid changes in the bones are, decalcification, the formation of cyst-like cavities and resorption of the bony tissue of the trabeculae and shaft which become largely replaced by fibrous tissue (fig. 279). His-

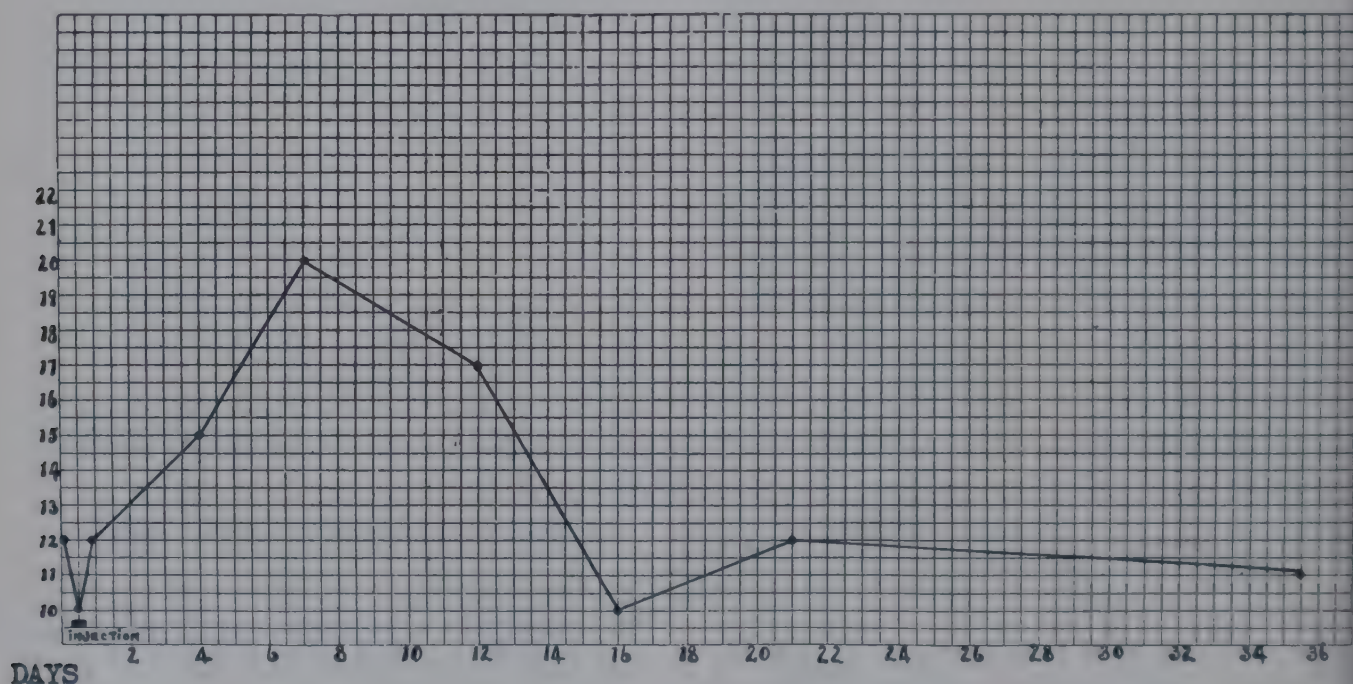


FIG. 278. Serum calcium curve of a dog illustrating the effect of a large dose of irradiated ergosterol given intravenously in divided doses over a period of four hours. Note the prolonged effect upon the serum calcium. (A. Taylor, Weld, Branion and Kay.)

larly resistant to overdosage with irradiated ergosterol. It has been shown by others that either parathormone or irradiated ergosterol gives rise to metastatic calcification and to bony changes analogous to osteitis fibrosa cystica.⁵ Irradiated ergosterol, however, takes longer to show its effect upon the serum calcium than does parathyroid extract, and the hypercalcemia once established persists for some weeks (fig. 278).

Two other dissimilarities in the action of vitamin D and of the parathyroid hormone have been reported. Whereas, the hormone increases the reabsorption of phosphate by the renal tubules, vitamin D has the opposite effect. The vitamin,

⁵ Selye finds that the histological picture of the bone in the rat after parathormone differs from that resulting from overdosage with irradiated ergosterol.

logically a great increase in the number of osteoclastic elements (p. 714) is seen. The condition was shown by Mandl in 1926 to be due to adenoma of a parathyroid gland. Its chief clinical features are, (1) pain in the bones. (2) Hypotonicity of the muscles. (3) Elevation of serum calcium (sometimes up to 20 mg. per cent or but usually not above 15 or 16 mg.) (fig. 278) fall in plasma inorganic phosphorus (between 1 and 2 mg. per cent) and high plasma phosphate (4) Increase in urinary calcium, polyuria, high incidence of renal calculi; renal damage, peritubular calcium deposits leading to interstitial fibrosis, and cystic dilatation of the tubules (Anderson). The calcification appears to be secondary to a specific degenerative lesion. The mineral deposits in their turn induce further

damage of renal tissue. (5) Spontaneous fractures, deformity of the bones of limbs or spine, reduced and irregular density of the bones are evident under the X-ray. (6) A small tumor (parathyroid) may be palpable in the neck. In a case reported by Hunter a parathyroid tumor was found at operation behind the esophagus at the level of the second thoracic vertebra. In some instances the condition is due not to a single adenomatous tumor but to diffuse hyperplasia of parathyroid tissue (p. 729).

The treatment of the condition consists in locating and removing the tumor. The serum calcium falls abruptly after operation and frequently reaches a subnormal level; tetany of an intractable nature not uncommonly results. The cause of the abnormally low serum calcium is not easy to explain since it might be expected that the remaining healthy parathyroid tissue would be sufficient to maintain the serum calcium at the

in turn of phosphate retention and hyperphosphatemia (see renal rickets, p. 718).

CALCIUM METABOLISM

Calcium is an indispensable mineral; it is a constituent of all animal fluids and solid tissues; it plays an important rôle in a number of physiological processes and conditions. The most obvious of these are: (a) coagulation of the blood (p. 88), (b) formation of bone (p. 713), (c) cardiac rhythmicity (p. 158), (d) maintenance of normal neuromuscular excitability (p. 704), (e) milk production (p. 768), (f) membrane permeability (p. 25).

THE DISTRIBUTION OF CALCIUM IN THE BODY

Calcium constitutes about 2 per cent of the weight of the adult body and about 99 per cent of the total quantity is contained in the skeleton. The muscles contain about 8 mg. per 100 grams of

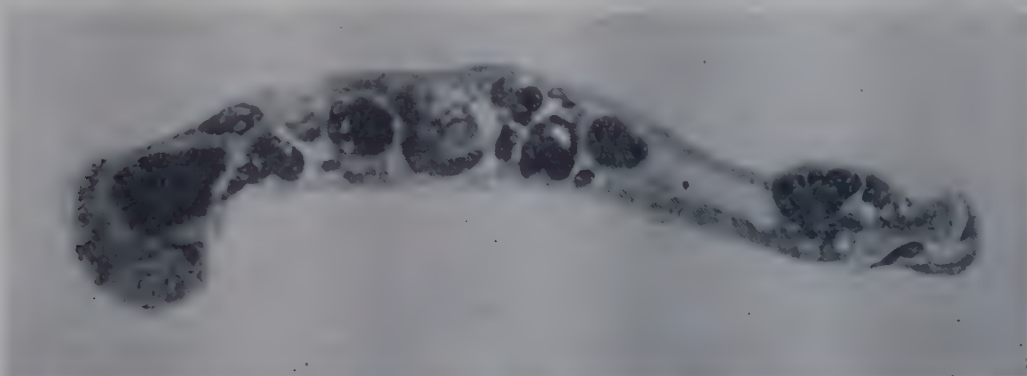


FIG. 279. Showing section of humerus from case of generalized osteitis fibrosa cystica. (From Hunter and Turnbull after Hill and Lucey.)

normal level. The phenomenon is probably due to the persistence after operation of a compensatory depression of activity in the other parathyroids which had resulted from the excess hormone discharged by the adenomatous gland. Bodansky and Jaffe found, for example, that in animals, hypocalcemia followed the termination of a prolonged course of parathormone injections.

Parathyroid hyperplasia may be induced experimentally by the following means (a) low calcium diet (rats and rabbits), (b) lack of vitamin D (chicks), (c) daily injections of phosphate over a period of weeks, (d) surgical reduction of renal tissue, or experimental nephritis; the former procedure produces dwarfing in rats and a condition resembling the renal rickets of children (Pappenheimer). In the human subject hyperplasia of parathyroid tissue may occur in association with chronic nephritis, in which event the parathyroid enlargement may be a compensatory reaction to the hypocalcemia which is the result

wet weight, plasma or serum from 9 to 11.5 mg. per cent. The red corpuscles contain only minute amounts; the content of the whole blood is,

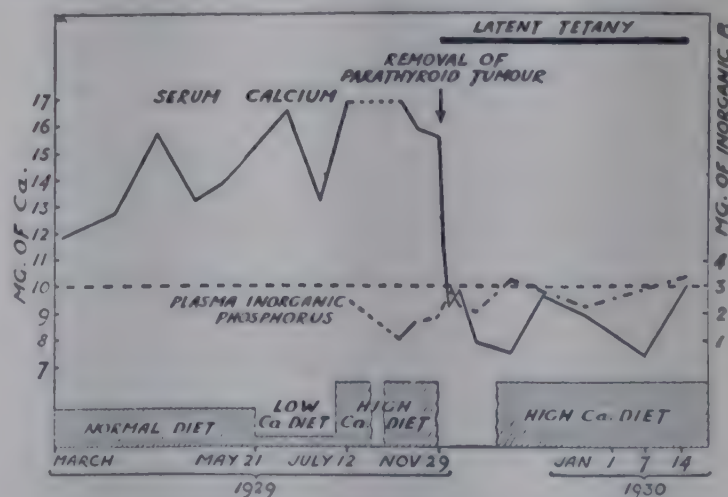


FIG. 280. Showing chemistry of blood in hyperparathyroidism, and the effect of removal of the parathyroid tumor. (After Hunter.)

therefore, between 4.5 and 6 mg. per cent. The other body fluids, e.g., lymph, aqueous humor, ascitic and edema fluids, etc., contain it in some-

what lower concentration, while the concentration in the cerebro-spinal fluid is only about 5 mg. per cent. Negligible amounts of calcium are deposited in the skeleton before the fifth month of intra-uterine life, and over 60 per cent of the skeletal calcium of the new-born is the result of deposition during the last two months of prenatal life (fig. 281).

THE STATE OF THE CALCIUM IN THE BLOOD

Practically all the calcium of blood, as just mentioned, is contained in the plasma; after clotting it is all present in the serum, and it is upon this that determinations are usually made.

The clot itself contains mere traces. The calcium of blood exists in two forms, *non-diffusible* and *diffusible*. The non-diffusible form is bound to serum protein (chiefly to the albumin fraction). It remains in the serum when the latter is dialyzed or subjected to ultra-filtration (i.e., filtration of the serum through a collodion membrane by the application of hydrostatic pressure). The non-diffusible part constitutes about 45 per cent (from 4 to 5 mg. per 100 cc.) of the total serum calcium. The diffusible portion amounts to 55 per cent or so (5 to 6.5 mg. per 100 cc.) of the total calcium; when the serum is ultra-filtered this fraction passes into the filtrate. *Nearly all the diffusible calcium of the serum is in ionized form.* The previous low figures which have been given for the concentration of ionized calcium (1.5 to 2 mg. per 100 cc.) are, according to McLean and Hastings erroneous. They state that a very small amount of diffusible unionized calcium (about 0.25 mg. per 100 cc.) is present in the form of a citrate-like compound. The ionized calcium is in the form of calcium carbonate and phosphate. The following is a summary of the calcium fractions in serum.

Serum calcium:	mg. per 100 cc.
Non-diffusible.....	4.0 -5.0
Diffusible.....	5.0 -6.5
Ionized.....	4.75-6.25
Unionized	0.25

The non-diffusible calcium, as might be expected, varies with the protein concentration of the plasma. For example, in Bright's disease (without phosphate retention) the decline in serum calcium roughly parallels the fall in plasma albumin and the hypocalcemia is due mainly to a reduction in the non-diffusible fraction. Lymph which has a lower concentration of protein than plasma also has a lower calcium content.

The calcium of the cerebrospinal fluid, which is

practically protein-free, is almost entirely in the diffusible form, and has a concentration approximately equal to that of the diffusible fraction of the plasma. The calcium concentration of the cerebrospinal fluid has, therefore, been taken as an index of the diffusible fraction of the plasma calcium upon the assumption that the former fluid is simply an ultra-filtrate. This assumption is not warranted, since it is more probable that the cerebrospinal fluid is *secreted* by the choroid plexus (p. 933). Also, the administration of parathyroid extract or the injection of calcium salts, both of which raise the diffusible calcium of the plasma, causes little increase in the calcium concentration of the cerebrospinal fluid; it is little affected by parathyroidectomy.

McLean and Hastings have devised a biologic method for the determination of the ionized calcium of body fluids based upon the sensitivity of the frog's heart to the calcium ion concentration.

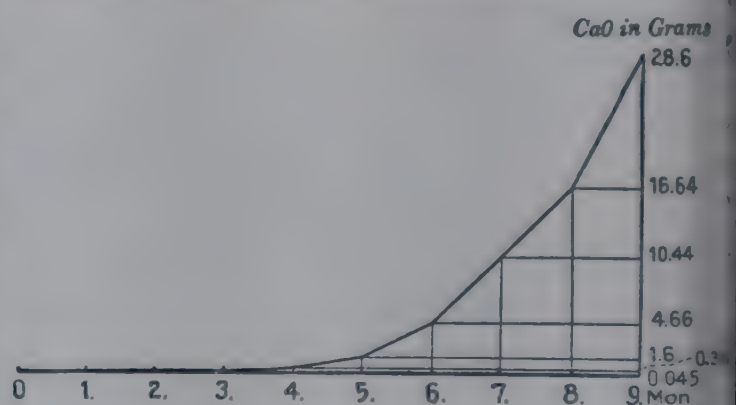


FIG. 281. Showing the increase in the calcium of human fetus in later months of gestation. (From Hastings after Schmitz.)

In this method the amplitude of the contraction of the isolated heart is recorded upon a moving drum. A cannula (a modified Straub cannula) is passed through the aorta into the ventricle and tied in position. A series of calcium chloride solutions graded in concentration by 0.1 millimoles per liter is made up. The cannula is filled with the unknown fluid (serum, edema fluid, cerebrospinal fluid, etc.) and the amplitude of the heart contraction recorded. The cannula is then emptied and refilled with one of the standard solutions. If the amplitude of contraction given with the latter is greater than that given by the unknown solution a standard solution of lower concentration is tried, if the contraction amplitude is less the cannula is filled with a more concentrated solution. The calcium solution giving a contraction which just matches that given with the unknown fluid is taken as having the same concentration as the unknown.

McLean and Hastings state that the ionization of calcium in the body fluids is determined primarily by an equilibrium between calcium and protein which may be expressed by the following equation:

$$\frac{(\text{Ca}^{++}) \times (\text{Prot}^{-})}{(\text{CaProt})} = K$$

$$= 10^{-3.22} \text{ (at a temperature of } 25^{\circ}\text{C. and pH 7.35)}$$

In other words, they consider that the calcium in protein-containing fluids is present as calcium proteinate which ionizes as a weak electrolyte into calcium and protein ions, with a residue of the protein-bound calcium, i.e., of the non-diffusible calcium fraction. They state that, knowing the protein and total calcium concentrations, the calcium ion concentration in human serum or other protein-containing body fluid may be calculated from this equation.

THE ABSORPTION AND EXCRETION OF CALCIUM— CALCIUM BALANCE

Calcium is found in food as both organic and inorganic compounds, but probably it is absorbed only in the inorganic form. Absorption occurs mainly from the upper part of the small intestine. The reaction of the intestinal contents is an important condition in the absorption of this mineral, its salts, for the most part being readily soluble in acid but insoluble in alkaline media. Sugars, especially lactose, which yield organic acids in the intestine, favour absorption. Fats (free from vitamin D) reduce calcium absorption on a high Ca, low P intake, owing most probably to the formation of insoluble calcium soaps; but for some reason, perhaps the production of soluble complexes with fatty acids, such fats increase the absorption of calcium on a diet with a low Ca/P ratio. Protein food tends to increase the absorption of calcium since the latter forms soluble complexes with certain amino acids. Soluble calcium salts, such as the chloride, carbonate, lactate, and gluconate, but not the relatively insoluble phosphate, are readily and, in moderate dosage, almost completely absorbed. After the ingestion of a large dose of a soluble calcium salt, the serum calcium level rises, reaching its maximum value in about two hours. The normal serum concentration is reached again about three hours later. It is not possible to maintain the calcium level above normal by the administration of calcium salts.

Milk is the best dietary source of calcium, but important amounts (up to 0.2 gram daily) of available calcium may be obtained from "hard" drinking water. The calcium of many vegetables

is well utilized by the rat; the calcium of carrots (and probably of certain other vegetables as well) is readily absorbed by the human intestine, being nearly as valuable as that in milk. Spinach and other plant foods containing oxalic acid, which forms a relatively insoluble compound with calcium, reduce calcium absorption. In cereals (wheat, oatmeal), owing to their content of phytic acid (inositolhexaphosphoric acid) which combines with calcium to form an insoluble salt, much of the mineral is unavailable. The action of phytic acid in the intestine may depress the absorption of calcium of other food materials. Whole wheat flour has a higher phytic acid content than has white flour and, therefore, is a poorer source of absorbable calcium. As mentioned elsewhere (p. 656), the phosphorus of phytic acid is also largely unavailable. These facts explain the decalcifying action of certain cereals.



FIG. 282. Front and side views of skeletons of twin brothers (albino rats), one of which had received a diet of normal calcium content (Wheat, meat, and milk) while the other had received a low calcium diet (wheat and meat). (After Sherman and MacLeod.)

Calcium is excreted into the small intestine and in the urine; little or none is eliminated through the wall of the colon. The excretion of calcium continues upon a calcium-free diet or during a fast and, under these conditions, the body is in negative calcium balance. In man, on an ordinary mixed diet the calcium of the feces amounts to from 0.4 to 0.8 gram; this, though partly endogenous, is mainly the unabsorbable calcium of the food.

Smaller quantities of calcium are excreted in the urine and about 150 mg. are lost daily by this route. An increase or decrease in the absorption of calcium is reflected in parallel changes in the urinary excretion. The urinary calcium constitutes, therefore, a convenient index of calcium absorption.

The *calcium balance*, that is the difference between the quantity of calcium ingested and that

excreted in the urine and the feces, is *positive* (calcium retention) during *growth*, *pregnancy*, *acromegaly*, or after a period of *calcium starvation*. Sherman and Hawley found that children from three to thirteen years of age, upon a daily calcium intake of from 0.74 to 1.02 gram of calcium, utilized (i.e., retained) from 0.15 to 0.62 gram per day; the quantity retained was in proportion to the size of the child (0.01 gram daily per kilogram). In adults, Breiter and his colleagues found that the utilization of the calcium of milk varied from 15.3 to 30.3 per cent. The calcium balance is *negative* in *infantile rickets*, *celiac* and *renal rickets*, *sprue*, *osteomalacia*, *hyperparathyroidism*, *hyperthyroidism* (pp. 675, 708), during *starvation* or *calcium deficiency*, and usually during *lactation*. In infantile rickets (p. 652), celiac rickets, and osteomalacia (p. 656), vitamin D administration reduces the negative balance, establishes calcium equilibrium or induces a positive balance. There is some uncertainty regarding the mode of action of vitamin D upon calcium absorption in normal animals. Some authorities believe that it increases the absorption of calcium but others maintain that its action in this regard is negligible and that its chief action is upon the deposition of calcium in the skeleton. Calcium metabolism is also influenced by vitamins A and C (p. 635 and p. 646). The daily calcium requirement and the calcium contents of various foods are given in chapter LVII, pp. 667 and 668, see also Fig. 282.

BONE

The composition of bone

Osseous tissue freed from fatty marrow is composed of organic material (mainly protein), water and minerals. The chief protein constituent is *ossein*, but there are also small quantities of *osseomucoid* and an *albuminoid*. Water constitutes about 25 per cent of the bone weight, organic material 30 per cent and inorganic constituents 45 per cent. The minerals consist of Ca, P, Mg, and small quantities of potassium, sodium, chlorine, fluorine and iron.

Calcium makes up from 15 to 18 per cent of the weight of fresh osseous tissue and from 20 to 25 per cent of the weight of bone which has been dried and extracted with ether.

Bone calcium exists in two forms, calcium carbonate— CaCO_3 —and tricalcium phosphate— $\text{Ca}_3(\text{PO}_4)_2$.⁶ The ash of bone amounts to about

⁶ Small amounts of calcium chloride and calcium fluoride are also present.

60 per cent of its dry weight. Calcium constitutes about 36 per cent of the ash, phosphorus about 16 per cent, magnesium 0.5 per cent and CO_2 5.5 per cent. The ratio of calcium to phosphorus is approximately 2.2 to 1. The ratio of *residual calcium* (i.e., calcium other than that present as carbonate) to residual phosphorus (phosphorus not combined with magnesium) is about 2 to 1. This is, approximately, the ratio of the two minerals in tricalcium phosphate. Magnesium is present mainly as $\text{Mg}_3(\text{PO}_4)_2$. The proportions of the three chief compounds in bone ash are $\text{Ca}_3(\text{PO}_4)_2$, 80 per cent, CaCO_3 , 13 per cent and $\text{Mg}_3(\text{PO}_4)_2$, 2 per cent. Some of the foregoing data are given in table 69.

Rickety bone contains a lower percentage of ash and larger proportions of water and organic material. The ratio of calcium to phosphorus, however, remains unchanged whether the rickety (experimental) develops upon a low calcium or a

TABLE 69
Calcium of bone (dog)

	IN WHOLE BONE		IN BONE ASH	C:P RATIO
	Fresh	Dry, ether extracted		
Total calcium (per cent)	18	25	36	2.2:
Residual calcium (per cent).....	31	2:

low phosphorus diet. The magnesium content of bone is said to be increased in rickets and in osteomalacia.

It is now generally believed that the calcium carbonate and calcium phosphate of bone are present not as separate compounds simply mixed together with smaller amounts of other mineral salts, but as a complex compound.

From a comparison of the refractive indices and X-ray diffraction patterns of bone and dental enamel on the one hand, and certain crystalline minerals composed mainly of calcium and phosphorus, Taylor and Sheard have concluded that the inorganic solid phase of bone and dental enamel resembles the apatite series (podolite, dahllite, fluorapatite, etc.). Fluorapatite, which is nearest in chemical structure to bone salt, has the following formula, $\text{Ca}_{10}\text{Fe}(\text{PO}_4)_6$. The predominant compound in bone is *hydroxyapatite*— $\text{Ca}_{10}\text{OH}(\text{PO}_4)_6$ —, the Fe atom in fluorapatite being replaced by OH. The bone salt is laid down in the form of minute crystals. Compounds in

which sodium, magnesium and other minerals are substituted for Ca are also found in bone.

The ratio of total calcium to phosphorus, 2.2:1 (or 10 atoms of Ca to 6 of P) and that of residual calcium to residual phosphorus, 2:1, (9 atoms Ca to 6 of P) which exist in bone also support this conclusion.

Pathological calcifications, e.g., salivary calculi, arterial or pulmonary calcifications, are believed to be similar in chemical composition to bone. Hastings and his associates hold a similar view in respect to a crystalline compound related to the apatite series as being the main mineral constituent of bone.

It is perhaps well to point out that adult bone is not simply an inert structural material but living tissue whose mineral composition fluctuates under the influence of other body functions. The trabeculae of the bone, as shown by Aub and associates, constitute a calcium store readily available when necessary for the maintenance of the calcium requirements of other tissues when the exogenous supplies are deficient. For this reason, though calcium continues to be excreted when an animal is kept, even for a long period upon a calcium-free diet, no change in the serum calcium level occurs. Parathyroid extract, as mentioned elsewhere, raises the serum calcium through its action in mobilizing these calcium stores.

In birds, the extraordinary demand made upon calcium metabolism for the production of the egg-shell has been provided for by the development of osseous tissue within the marrow spaces of the long bones. Weakening of the essential skeletal structure which otherwise might result from the withdrawal of the mineral during the egg-laying season is thus avoided. The growth of this so-called *medullary bone* is stimulated by estrogens. Normally, its growth appears to be under the control of the ovarian secretion; it is cyclical or seasonal in character, and is associated with other phenomena of the mating season of birds, e.g., the appearance of serum vitellin in the circulation, an increase in plasma fat and phospholipid, and pronounced hypercalcemia.

The bones also serve a detoxicating function, elements such as lead, radium, fluorine and arsenic, being removed from circulation and deposited in the bones and teeth. "Mottled enamel" (chalky white patches upon the surfaces of the teeth) is attributed to an excess of fluorine in the food or drinking water, though smaller amounts of fluorine are said to be beneficial for the

development of the teeth and to prevent dental caries. The mobilization of bone calcium plays a very minor rôle in maintaining the normal blood reaction against the ingestion or production of excess acid. Some reduction in bone calcium can be detected, however, in animals after the administration of hydrochloric acid.

Bone formation

THE HISTOLOGY OF DEVELOPING BONE. There are two types of ossification, *intramembranous* and *intra-*

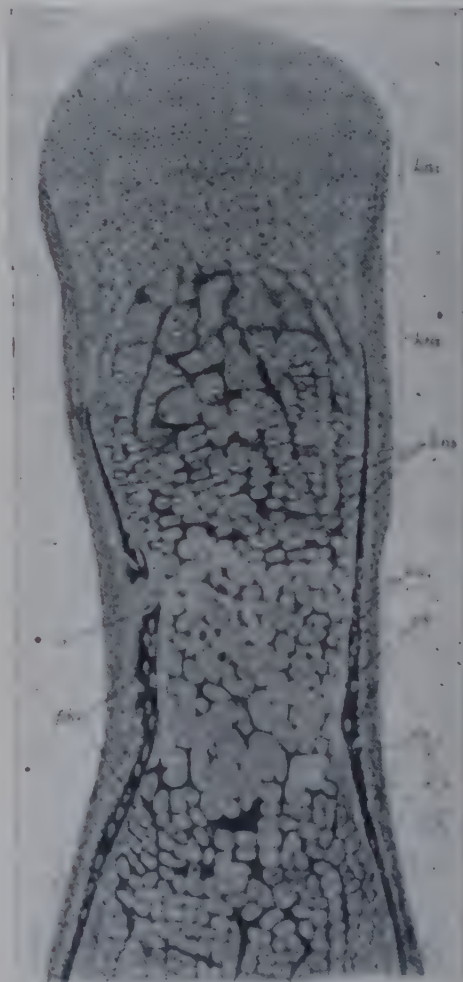


FIG. 283. Developing bone; proximal phalanx of a three-month human fetus. *kn*₁, unchanged cartilage; *kn*₂, columns of cartilage cells; *kn*₃, zone of calcifying cartilage; *kn*₄, vestiges of walls of broken down cartilage cavities; *ph*, perichondral (periosteal) bone (black); *ph*, perichondrium (periosteum);* connection between periosteum and primary marrow. As yet, no endochondral bone formation. (From Maximow and Bloom after Sobotta.) (See also p. 653.)

cartilaginous or *endochondral*. The bones of the cranial vault and the mandible are formed through the ossification of membranes. The bones of the limbs and trunk and the base of the skull are first modelled in cartilage which becomes transformed into bone by both endochondral and intramembranous (i.e., periosteal) forms of ossification. The development of a long bone of the limb, for example, starts with the deposition of calcium salts in the center of the shaft (*diaphysis*). From this *center of ossification*, as it is called, the process of calcification spreads toward each end of the bone (fig. 283). The cartilage cells just

ahead of the spreading zone of calcification show active proliferation, becoming arranged in longitudinal rows. The transformation of the calcified cartilage into true bone is brought about after the following fashion. The cells of the deeper layers of the membrane covering the cartilage—perichondrium—give off long processes to form a meshwork of interlacing fibers. These cells are referred to as *osteoblasts*. The fibrous framework thus laid down soon becomes impregnated with calcium salts with the formation of a layer of true bone just beneath the perichondrium, or periosteum as it must now be called. The subperiosteal process, which is essentially the same as that whereby the cranial bones are developed from membrane, is well advanced while the interior of the bone still consists merely of calcified cartilage. The latter, however, soon becomes invaded by blood vessels from the periosteum and by large multinucleated cells (20 to 40 μ) known as *osteoclasts*. These cells, which have a pronounced eroding action upon the mineralized cartilage, probably through the production of an enzyme, tunnel channels through it for the conveyance of the blood vessels and excavate small cavities. The excavations in which the osteoclasts lie are known as *Howship's lacunae*. Osteoblasts which have advanced into the interior with the blood vessels cause the formation of true osseous tissue in the walls of the spaces formed by the osteoclasts.

At a somewhat later date than that at which the primary ossification center appears in the shaft, a secondary or epiphyseal center appears in one or both ends of the bone. The calcification process and subsequent ossification follow the same course as that described for the diaphysis. The epiphyseal and diaphyseal areas, however, remain separated from one another by a layer of uncalcified cartilage, the *epiphyseal plate*, until a certain age, which varies between different bones.

Through the combined action of osteoclasts and osteoblasts a complete replacement of the calcified cartilage results and the structure characteristic of bone gradually evolves. The center of the shaft becomes hollowed out to form the medullary canal. The spaces which have been formed by the osteoclasts in the shaft of the bone itself become joined together and constructed into the system of *Haversian canals* which serve as conduits for the transmission of blood vessels. In the ends of the bones the spaces are much larger and irregular; and becoming filled with red marrow constitute the characteristic spongy or cancellous bone of this region. The walls of these spaces appear in cross section as interlacing bars of osseous tissue and are usually referred to as *trabeculae*. The bone forming the walls of the Haversian canals is laid down in a series of concentric tubular lamellae. As each lamella is completed it imprisons the osteoblasts within small lacunae from which numerous fine canals are given off; into these the processes of the osteoblasts penetrate. The osteoblasts in these situations lose their osteogenetic function but

do not disappear. In the developed bone they are referred to simply as *osseous cells* or *osteocytes*.

A long bone grows in length at the junction of the epiphyses with the diaphysis and in thickness through the activity of the osteoblasts of the deeper layers of the periosteum. The Haversian canals and the marrow cavity are also lined with a membrane—the *endosteum*—containing osteoblasts through which increased width of the bone is also brought about.

The osteoblasts and osteoclasts are concerned not only with the development and growth of bone, but are active throughout life and are responsible, it is believed to a large extent at any rate, for the lability of adult osseous tissue (p. 713). Healthy bone is constantly being broken down, resorbed and repaired. Several conditions may alter the balance one way or the other between these two processes, e.g., the relation of the calcium intake to the calcium requirement and the activities of various ductless glands—parathyroid, thyroid, pituitary, etc. Large numbers of osteoclasts are in evidence when bone resorption is taking place. Osteoclastic activity is therefore pronounced when remodelling of bone is occurring, as in the removal of excess callus or in the restoration to normal dimension of the enlarged end of a bone in healing rickets, in certain bone diseases, and in wasting diseases. In old age also, the resorptive process outstrips the processes of repair; the bones become rarefied (*senile osteoporosis*) and more fragile. Ham and some other authorities deny that the osteoclasts are active agents in the removal of the bone tissue, claiming that appearance of these cells is merely incidental or sequential to the resorption process.

When bone formation is in the ascendancy, as during the repair of a fracture, the osteoblasts show active proliferation.

Newly formed bone is stained selectively *in vivo* by madder, a red dye, or by alizarin, a derivative of it. These are therefore valuable agents for the investigation of the growth of bone in the living animal or of the action of parathyroid hormone and other influences upon bone metabolism. The dye, which is given orally is deposited with the mineral constituents, calcium and phosphorus.

A CONSIDERATION OF THE FACTORS UNDERLYING THE CALCIFICATION PROCESS. Several theories have been advanced in attempts to picture the processes underlying the deposition of calcium salts in the cartilaginous matrix. The four principal theories are as follows:

(1) A protein constituent of cartilage, it has been supposed, adsorbs calcium, for which it exhibits a special affinity; the calcium subsequently combines with phosphorus to form tricalcium phosphate. Wells showed, for example, that bone salts were deposited in a piece of boiled cartilage placed in the abdominal cavity.

(2) The saturation of a solution with a salt

such as calcium phosphate and the precipitation of the latter in solid form is determined by the product of the concentrations of the Ca^{++} and $\text{PO}_4^{=}$ ions in the solution, i.e., upon the *ion product* $[\text{Ca}^{++}] \times [\text{PO}_4^{=}]$; and not upon the total quantities of calcium and phosphorus present. The ion product at which the solution is just saturated is called the *solubility product*. The presence of protein in the solution reduces the degree of ionization, part of the calcium, as we have seen, becoming bound to form calcium proteinate, a weak electrolyte. The body fluids are therefore capable of dissolving more calcium phosphate than is a protein-free solution similar in its salt composition to that of plasma. The CO_2 dissolved in the body fluids also increases their ability to hold calcium salts in solution. Any reduction in the protein concentration or in the CO_2 tension in the body fluids would therefore be expected to favor the deposition of calcium salts.

An explanation of the calcification process upon a basis afforded by the foregoing considerations has been advanced by Howland. It is assumed that the fluids bathing the cartilage cells have, in common with other extravascular fluids, a lower protein concentration than has plasma. It is further suggested that since the cartilaginous matrix has a low metabolism, the CO_2 tension of the fluids bathing its cells is lower than that of plasma; the pH of these fluids will therefore tend to be higher. Such conditions it is argued must favor the deposition of calcium salts. A low concentration of inorganic phosphorus and of calcium in the plasma will, on the other hand, tend to retard calcification; this would be completely arrested if the ion product were below the value at which precipitation occurs. In practice Howland and his associates have employed the product of the *total* calcium and inorganic phosphorus, each expressed in milligrams per cent, as an index of the calcification process in infantile rickets. They state that in children with active rickets the product is practically always below 40, and when the disease is severe, below 30, whereas in normal children it is between 50 and 60 (i.e., $\text{Ca } 11 \times \text{P } 5 = 55$). It is obvious that a fall in either inorganic phosphorus or calcium would tend to lower the $\text{Ca} \times \text{P}$ product; actually two varieties of rickets were distinguished—a low phosphorus and a low calcium type. It is now recognized, however, that these are simply different stages of the disease and that the level of the inorganic phosphorus alone is a more useful

criterion by which to judge the extent of the calcification defect than the $\text{Ca} \times \text{P}$ product. For example, when rickets is progressing the inorganic phosphorus of the plasma is lowered to between 3 and 4 mg. or less per cent, but the serum calcium is not far from the normal level. During the stage of healing, i.e., of active calcification, the inorganic phosphorus tends to rise and the serum calcium to fall (p. 704); there might therefore be little change in the $\text{Ca} \times \text{P}$ product.

Another factor considered to be of importance in the calcification process is the *supersaturation* of the body fluids with calcium salts. That is, quite apart from the greater solubility of calcium salts in fluids containing protein and CO_2 , the concentrations of calcium phosphate and calcium carbonate in the body fluids are constantly maintained above their saturation limits, owing to the extreme slowness with which final equilibrium between the solid and liquid phases is established. Precipitation of these salts from solution will continue so long as the ion product is above that of the saturation level.

Calcification, however, cannot be explained upon a physico-chemical basis alone; the activity of living cells is also involved in the process. Shipley, Howland and Kramer showed, for example, that in experiments *in vitro* calcification was inhibited by a protoplasmic poison such as HCN. Two views have been expressed as to the nature of the vital processes concerned.

(3) Watt, from a comparison of the shapes of calcium phosphate particles precipitated in certain inert colloids with those formed in bone, concluded that calcification was not a simple precipitation of calcium phosphate from solution but was due to the active *secretion* by the osteoblasts of bone salts derived from the calcium and phosphorus of the blood.

(4) According to Robison and his colleagues, calcification is primarily dependent upon enzyme action through which the fluids in immediate relation to cartilage cells become highly supersaturated with calcium phosphate. These observers have accumulated much evidence in favor of their view. They have demonstrated the presence in bone (and also in plasma and other tissues, see below) of an enzyme capable of hydrolyzing various phosphoric esters, e.g., hexose-monophosphate, glycerophosphate, etc. This enzyme is called *phosphatase*. It is believed to be a product of the osteoblasts, the proliferating cartilage cells and the cells of the inner layer of the periosteum. According to this conception

of the calcification process the enzyme liberates inorganic phosphate from phosphoric esters and raises, locally, the concentration of the $\text{PO}_4^{=}$ ion. The product of the concentrations of the Ca^{++} and $\text{PO}_4^{=}$ ions then exceeds the solubility product of calcium phosphate, which is in consequence deposited in the cartilagenous matrix.

Evidence bearing upon this hypothesis is as follows:

(a) It was shown by Robison that when the head of a bone from a rachitic rat was immersed in a solution of calcium hexosemonophosphate at body temperature a deposit of calcium phosphate occurred in the zone of preparatory calcification (p. 653). This was attributed to the liberation by phosphatase of inorganic phosphate from a phosphoric ester, thus raising the product of the concentrations of $\text{PO}_4^{=}$ and Ca^{++} ions.

(b) Shipley, Kramer and Howland found that calcification of a rachitic bone occurred if placed in normal serum. Calcification also resulted if the bone were placed in a sterile solution of inorganic salts containing sodium chloride, sodium bicarbonate and magnesium sulphate, together with calcium and inorganic phosphate in the same concentrations as in normal serum. They concluded that living processes were concerned, since calcification was inhibited by HCN. They believed, however, that phosphatase could have played no part in the process for the artificial solution did not, of course, contain a phosphoric ester.

(c) Robison claimed that the result of the experiment just described was dependent upon the fact that in the solution used the concentration of the calcium phosphorus compound was near the point at which spontaneous precipitation might be expected to occur. In normal plasma, as already mentioned, calcium and phosphorus remain in solution at these concentrations because it contains protein which depresses the ionization of calcium; the ion product upon which precipitation depends is therefore considerably lower. Robison and Soames showed that calcium phosphate precipitates after a few days from a solution such as that employed by Shipley and associates if simply allowed to stand. It was found indeed by the latter workers that the addition of protein to the extent of 1 or 2 per cent, inhibited the calcification of the immersed bone. Robison and Soames showed later that though calcification of rachitic bone will occur when immersed in a solution containing calcium and phosphorus if the concentrations are sufficiently high, i.e., $\text{Ca} \times \text{P}$ product over 40 (4 mg. P and 10 mg. Ca per 100 cc.), calcification will not occur if the product is lower than this unless a phosphoric ester is added. Quite small amounts of the ester (glycerophosphate) were sufficient to cause calcification.

(d) Phosphatase is present in bone in largest amounts when and where active calcification is taking place (see

below) which strongly suggests that it plays an essential rôle in the calcification process.

(e) Certain facts have been cited as opposed to the phosphatase hypothesis: (a) in rickets the phosphatase activity of bone and plasma is increased rather than the reverse, and in the blood of rachitic rats the percentage of phosphoric esters hydrolyzable by phosphatase is not below normal. (b) Normal plasma contains only very small quantities of phosphoric ester which seem inadequate to supply the inorganic phosphate necessary for the calcification process. (c) Certain tissues which do not calcify normally are rich in phosphatase while other tissues such as the arteries which are frequently the site of pathological calcification, do not contain the enzyme.

Robison does not contend, however that the phosphatase mechanism is the only one concerned in the calcification process for, as mentioned above, calcification will occur in the absence of a phosphoric ester provided the concentrations of calcium and inorganic phosphate are sufficiently high. He and his colleagues found that when bone slices were treated with KCN or with certain fat solvents (alcohol, chloroform or acetone) before placing them in the supersaturated solution, calcification did not occur in the absence of glycerophosphate. These substances, however, exerted little or no inhibitory effect if glycerophosphate were present, i.e., the phosphatase mechanism was not paralyzed and calcification proceeded. Formalin, on the contrary, prevented calcification whether a phosphoric ester was present or not. These results, in Robison's view, point to two distinct mechanisms governing the calcification process. (a) The phosphatase mechanism, poisoned by formalin, which produces in the fluids bathing the cartilage cells a state of supersaturation in respect to bone salt. (b) A mechanism poisoned by several agents, especially cyanide, which is responsible for the deposition of bone salts from a supersaturated solution, whether this is the result of phosphatase action or is brought to the cartilage matrix from another source. The nature of the second mechanism is unknown. It may be due, Robison suggests, to a "slight increase in the pH of the matrix fluid brought about by some membranous equilibrium." Since this mechanism is inhibited or paralyzed by cyanide it is evidently dependent also upon the activity of living cells.

The distribution and properties of phosphatase

Phosphatase is present in greatest amounts in ossifying cartilage, in smaller amounts in forming bone, but is absent from resting epiphyseal cartilage and from non-ossifying cartilage in other situations. It was shown by Robison to be absent from the patella before the appearance of the ossification center in this bone but present thereafter. The teeth of young animals contain

in relatively large amounts. It is present in milk⁷ and also in the floral parts of plants.

The optimum pH for phosphatase activity is round 9.0. Magnesium greatly increases the activity of the enzyme, whereas calcium ions are mildly inhibitory. Phosphatase activity has been demonstrated in a number of tissues (see table 70).

TABLE 70*

Relative phosphatase activity of tissue extracts prepared under similar conditions from various mammalian tissues

	REFERENCE					
	Forrai (1923)	Robinson (1923)	Kay (1928, 1)			Kay (1931, 2)
	Man	Young rabbit	Adult			Adult rat—average of 4
			Rabbit	Cat	Man	
Tissue:						
Intestine.....	100					
Duodenum...			50†	93†	57†	46
Jejunum.....			100†	100†	85†	33
Ileum.....			53†	81†	100†	15
Colon.....			17†	34†	27†	6
Kidney.....	58	36	33	38	35	100
Ossifying cartilage.		100				
Whole bone.....			20	10		76
Liver.....	16	43	12	4	6	4
Pancreas.....	8	11				
Lung.....			10	26	7	20
Blood.....		14				1
Testis.....	12					13
Brain cerebrum...			3	3	4	7
Cardiac muscle....			1	1		5
Skeletal muscle....		4	1	1		2
Artery.....				Nil	Nil	

* Modified from H. D. Kay, Phys. Rev. 1932, 12, p. 388.

† Mucosa only.

The figures in each column are relative one to the other, but the different columns cannot be compared quantitatively.

The enzyme in plasma and probably that of kidney and intestine are identical with that found in bone.⁸ Bone is apparently the main

⁷ Kay and Graham have introduced a test by which one may determine whether a given sample of milk has been properly pasteurized. The test is based upon the fact that the temperature used in the pasteurization process destroys the activity of the enzyme.

⁸ Phosphatase activity is expressed as the number of mg. of inorganic phosphorus liberated per gram of tissue from sodium β-glycerophosphate after 48 hours hydrolysis at the optimum pH and at a temperature of 38°C.

if not the sole source of plasma phosphatase, since this is not appreciably reduced after the removal of various organs (intestine, kidney, spleen, pancreas, etc.). Phosphatase is excreted by the liver; a marked rise in plasma phosphatase therefore occurs in obstructive jaundice and in jaundice due to liver damage, but not in the purely hemolytic type.

The following phosphoric esters are hydrolyzed by bone phosphatase—hexosediphosphoric ester (of Harden and Young); phosphopeptone from

TABLE 71*

Changes in the phosphatase content of the plasma in disease

DISEASE	NUMBER OF CASES	PHOSPHATASE CONTENT OF PLASMA		
		Highest	Lowest	Mean
		units	units	units
Arthritis without bony changes.....	11	0.33	0.11	0.17
Arthritis with bony changes.....	7	0.25	0.09	0.17
Exophthalmic goiter... {	7	0.75	0.27	0.47
	8†	0.53†	0.19†	0.36†
Osteomyelitis.....	8	0.41	0.14	0.27
Fragilitas osseum (infants or children).....	6	0.66	0.16	0.41
Acromegaly.....	2	0.32	0.22	0.27
Rickets (infantile)†.....	13	1.7	0.42	1.03
Rickets (renal).....	2	1.5	0.9	1.2
Adolescent rickets.....	1			>2.4
Osteitis fibrosa (generalized)..... {	3	>2.5	1.5	>1.8
	3†	1.8†	1.06†	>1.3†
Osteitis deformans.....	24	3.4	0.65	>1.7

* Modified from H. D. Kay, Phys. Rev., 1932, 12, 412.

† Hunter (1930).

‡ Average for normal infants of approximately same age = 0.32 arbitrary unit. Average for normal adults = 0.10–0.21 unit.

casein; guanylic and adenylic acids of yeast nucleic acid; pyrophosphoric acid; and fructose phosphoric acid. Inosinic acid and pyrimidine nucleotides (p. 564) are hydrolyzed by intestinal and kidney phosphatase and also probably by bone phosphatase.

The significance of the presence of phosphatase in kidney, intestine and tissues other than bone is obscure. The pathological calcification of arteries such as the aorta, which Kay states does not con-

tain the enzyme, cannot be satisfactorily explained upon the phosphatase hypothesis.

The phosphatase in bone and the other solid tissues mentioned is reduced by the administration of irradiated ergosterol in amounts which cause the withdrawal of calcium from the bones and calcification of the tissues, whereas small doses cause an increase. On the other hand, it has been shown by Kay that the plasma phosphatase is increased, often markedly, in diseases involving extensive changes in bone structure (see table 71).

DEFECTS OF OSSIFICATION AND PATHOLOGICAL CALCIFICATIONS

Diseases of bone

Several of these have been considered in other parts of the text—*rickets* in Chapter LVI and on page 712; *osteomalacia* on page 656, *celiac rickets* on page 657, and *osteitis fibrosa cystica* on page 708.

The hardness, strength and rigidity of healthy bone depend upon the proportions of the organic and inorganic constituents incorporated into its structure, much as the properties of a plaster bandage depend upon the impregnation of the cotton mesh with plaster of Paris. The mineral and fibrous components are of equal importance; each reinforces the other. The cotton bandage has a certain tensile strength but lacks rigidity; a cast of plaster of Paris alone has maximum rigidity, but is brittle and readily broken or crushed. In most bone diseases the normal proportions between these two components are altered. In rickets and osteomalacia, for example, the bone salts are reduced in relation to the organic material. In these diseases, as also in osteitis fibrosa cystica, the bones are in consequence softer and more yielding than the normal. In certain other bone conditions the proportion of mineral to organic material is increased. The bone as a result is brittle and easily fractured. In other instances again there may be little change in the proportion of these two materials but the mass of the bone is increased or diminished with corresponding variations in strength.

Osteitis deformans (*Paget's disease*) is a disease of the skeleton involving mainly the bones of the skull, pelvis, limbs and spine. The cranium is enlarged and its wall greatly thickened, the long bones of the limb are massive and curved, the back is bowed (kyphosis) and its movements restricted. The organic matter of the bones is increased and the calcium content decreased, but

the total amount of phosphorus is not far from normal. A pronounced degree of arteriosclerosis is frequently a feature. Metabolic studies in the disease have yielded little information, though there is said to be a retention of calcium and phosphorus.

Fragilitas ossium (*osteogenesis imperfecta*) is a congenital disease characterized by thinness and extreme fragility of the skeleton, especially of the long bone and ribs. The cranium shows defective calcification. Fractures result from the most trivial injuries or may occur without any apparent cause. Union and healing of the fractures occur, however, as readily as in a normal bone. The bones have a low calcium content, the cortex is very thin and the medullary cavity dilated.

Achondroplasia is a congenital disease in which endochondral ossification (p. 713) of the limb bones especially the humeri and femora, is defective. Periosteal ossification is active. The long bones are therefore much shorter and thicker than normal, strong and dense. A characteristic type of dwarf results—short arms and legs with a trunk and head of almost normal dimensions. The bones of the base of the skull fuse prematurely and the development of certain facial bones is abnormal. Achondroplastic dwarfs develop as a result of these abnormalities a distinctive facies—depressed nasal bridge (pugnose), broad forehead and prominent lower jaw.

The cause or causes of the three foregoing osseous abnormalities is unknown. The possibility of some endocrine disorder, of course, comes to mind, but there is little or no evidence of such.

Marble or chalky bone (*Albers-Schönbergs disease*). In this condition the density of the bone is greatly increased; the cancellous tissue is filled with a chalky material and the medullary canal may be almost obliterated by the concentric thickening of the shaft. The excessive calcification, however, renders the bone soft and brittle. Calcification of soft tissues—arteries, lungs, tendons—is often a feature. The disease is exceedingly rare and is mentioned here only because of the interesting possibility that some abnormality of parathyroid function is responsible. A case has been reported by French observers in which there was enlargement of the parathyroids, and Selye has produced in rats a state of increased bone density, which he considers comparable to this disease, by the administration of parathyroid extract after the animals had become tolerant to the usual action of the hormone.

Renal rickets. This is a condition commencing most usually in childhood and associated with chronic nephritis, rarefaction of the skeleton, dwarfism, low serum calcium and sometime calcium deposits in the soft tissues and especially in the kidneys. The parathyroids usually show hyperplasia. We have seen that a rise in serum phosphate causes a reciprocal reduction in serum

calcium and it is generally held that the hypocalcemia seen in this disease is due to the retention of phosphate resulting from the renal insufficiency. The hypocalcemia so produced causes, it is presumed, a drain of calcium from the bones. Increased excretion of phosphate into the intestine is a result of the diminished excretion by the kidney, with consequent depression of calcium absorption (p. 711) is probably a contributory factor in the production of the low serum calcium. Albright and his colleagues suggest that renal osteitis fibrosa cystica (p. 708) is a more appropriate name for this disease than renal rickets inasmuch as the histological changes in the bones are indistinguishable from *primary* hyperparathyroidism. This brings up the question as to whether the demineralization of the skeleton is due to the hyperparathyroidism induced as a compensatory reaction to the low serum calcium, caused in turn by the phosphate retention, or whether the bone changes and parathyroid hyperplasia are independent results of the hypocalcemia. No definite answer can be given to this question. Obviously, since kidney disease not infrequently results from hyperparathyroidism (p. 708) and parathyroid hyperplasia may occur in chronic renal disease, it is very difficult if not impossible in a given case (especially if the subject is an adult) to decide whether the parathyroid abnormality is a primary or a secondary factor.

Calcification of soft tissues

DYSTROPHIC CALCIFICATION is the term applied to the deposition of calcium salts in dead, dying or chronically inflamed tissues and in areas of fatty or hyaline degeneration. Thus areas of necrosis, infarcts, scar tissue, caseous tuberculous areas and degenerated nerve cells, tend to undergo calcification. Calcification also occurs in the infarcts of the placenta which appear in the later half of pregnancy. Many of the examples of pathological calcifications to be described are simply special examples of dystrophic calcification. The factors determining the deposition of calcium salts in devitalized tissues are obscure. It has been suggested that since the CO_2 production in such tissue is minimal or entirely absent they will have a more alkaline reaction; this, of course, would tend to cause the deposition of calcium salts.

CALCINOSIS is the name given to conditions in which (a) calcified areas are scattered throughout the skin and subcutaneous tissues (*calcinosis circumscripta*), or (b) a more generalized calcification of skin, interstitial tis-

sues, tendons, fascia or muscles occurs (*calcinosis universalis*). When the calcification process involves predominantly the interstitial tissues of the muscles the condition is usually referred to as *myositis ossificans*. In calcinosis the calcium and phosphorus levels of the blood are normal. Metabolic studies have in some instances revealed a retention of calcium. In the region of the calcified areas true bone formation may occur. Calcinosis of the superficial tissues is in many cases associated with scleroderma (a condition characterized by induration of the skin due to an increase in the intercellular collagenous tissue). The cause of calcinosis is obscure; the calcification process may be secondary to degenerative changes in the tissues themselves. There is no evidence that it is dependent upon an abnormality of parathyroid function, though Selye has reported a condition in rats resembling scleroderma following the administration of parathyroid extract.

ARTERIAL CALCIFICATION. (1) *Arteriosclerosis* is seen in three main forms: (a) the *atherosclerosis* (atherē = crushed grain, porridge) of *Marchand*, (b) the *medial sclerosis of Mönckeberg*, and (c) *diffuse hyperplastic sclerosis* involving the arterioles. In the first two of these forms but not in the last, calcification plays a prominent rôle.

In *atherosclerosis* the aorta and its branches are the principal sites of the disease. The most noticeable changes occur in the intima, though degeneration of the elastic tissue, fibrosis and calcification of the media are also seen. The endothelial cells lining the vessel show hyperplasia, the thickened intima later undergoing hyaline or fatty degeneration; the fatty or atheromatous areas, which actually consist of deposits of cholesterol esters, finally become calcified. Calcareous plaques are thus formed upon the intima of the vascular wall. According to Klotz, calcium first combines with fatty acids in the degenerated area to form a calcium soap; the deposition of calcium phosphate and calcium carbonate occurs later. The pronounced tendency for calcification to occur in areas undergoing fatty change, e.g., in degenerating lipomata and in fat necrosis, support the conception that saponification precedes the deposition of lime salts. Objections have nevertheless been raised against the view that soap formation is a necessary preliminary, in all cases at any rate, to the calcification process. Wells states that calcium soaps cannot be extracted from arterial tissues undergoing fatty changes even very early in the degenerative process, but calcium phosphate and carbonate are present from the start. In addition, calcium soaps introduced into the tissues are removed and not transformed into calcium phosphate and carbonate.

It is believed by some observers following the theory of Thoma that the onset of the degenerative changes is secondary to deterioration of the elastic tissue of the intima and media, which by weakening the arterial wall permits distention of the vessel. The stretching interferes, it is presumed, with the blood supply of the vascular wall; the intimal thickening is looked upon as a compensatory process. Klotz, on the contrary, considered the intimal proliferation as a primary process due possibly to a toxic agent.

In medial sclerosis the degenerative changes are situated predominantly in the media of the vessels of the extremities. Degeneration of the elastic tissue and fibrosis of the smooth muscle occur, followed by calcification of the degenerated tissue. The vessels are converted into relatively rigid tubes—the so-called “pipe stem” arteries. The mineral tends to be laid down in rings encircling the vessel, which has suggested a comparison with the artery to a “goose’s trachea.”

The degeneration of the elastic tissues of the arteries which is such a prominent feature, and possibly the primary change, in both types of the disease is attributed to “wear and tear”—the repeated stretchings and recoils of the arterial wall—and to the inherent tendency for elastic tissue in general to deteriorate with age. Arteriosclerosis in one or other of the two types just described is, therefore, a disease of advancing years or is brought on prematurely by the excessive arterial strain caused by arterial hypertension (p. 135). The diffuse hyperplastic type (c) is, however, more characteristically a consequence of hypertension.

Arterial calcification may be looked upon simply as a particular type of dystrophic calcification and not specific in nature.

(2) *Arterial calcification associated with disturbances of calcium metabolism.* Calcium deposition in the arterial walls is often a pronounced feature of metastatic calcification; this is described in the next paragraph.

METASTATIC CALCIFICATION. This term implies a transference of calcium from the skeleton to the soft tissues. It occurs in animals treated with excessive doses of parathyroid extract or irradiated ergosterol. Though the calcium deposits may be found in any of the soft tissues, the arteries, kidneys and lungs are especially susceptible to calcification. The fundus of the stomach is also a common site. It will be noted that the three last-mentioned organs eliminate acid; and it has

been suggested that since this will leave the blood more alkaline in reaction, a condition favorable to calcium deposition is created. Metastatic calcification also occurs occasionally clinically. It has been reported in hyperparathyroidism (p. 708), renal rickets and in certain bone diseases e.g., multiple myelomata. It is very natural to assume that in conditions of disturbed calcium metabolism and destructive disease of bone the calcium deposits are simply the result of the excessive calcium in the circulation. It is quite possible, however, that, in some instances at any rate, it is secondary to tissue injury and may therefore be, in reality, a type of dystrophic calcification induced by a toxic agent. Parathyroid extract and irradiated ergosterol, for example, besides their effects upon calcium metabolism have a definitely toxic action. Furthermore, metastatic calcification is in some instances associated with hypocalcemia.

It is a fact of great interest that the calcium deposits in the arteries and in other soft tissues in the various types of pathological calcification have the same composition as the main mineral compounds of bone. Evidence obtained by both chemical and physical methods support this conclusion. In certain instances actual bone formation occurs, even to the extent of producing red marrow tissue. Areas of ossification have been observed in the aorta and in the neighborhood of calcium deposits in the necrotic kidney of the rabbit. Also, as shown by Huggins, if a section of the mucosa of the bladder be transplanted into the subcutaneous tissues it becomes the site of bone formation.

Renal calculi (nephrolithiasis, urolithiasis)

Kidney and bladder stones composed largely of calcium phosphate have been produced in experimental animals (rats) by the administration of irradiated ergosterol in excess. They are apparently the result of the excretion in the urine of large amounts of calcium liberated from the bone. Renal or vesical calculi are also associated with various bone diseases of a destructive nature; they are quite frequent in hyperparathyroidism. The great majority of renal calculi arise, however, unassociated with any other disease and a large proportion of them are composed of other materials than calcium phosphate (e.g., uric acid, urates, oxalates, cystine, etc.). Nephrolithiasis is particularly prevalent in the tropics and the

sibility has been suggested that hypervitaminosis D, due to over-irradiation with ultraviolet light and, possibly, deficiency of vitamin A are causative factors. The production of renal calculi in animals by hypervitaminosis D, as mentioned above, occurs only, however, when hormones are employed which cause bone resorption and an increased concentration of calcium in the urine. Such results have therefore little bearing

upon the question of the production of urinary calculi in the human subject. Also, though there is some evidence that avitaminosis A is conducive to the development of urinary calculi in animals (the cornification of the epithelium of the urinary tract being, apparently, a predisposing factor), there is little warrant for applying the results of animal experiments to the question of urinary lithiasis in man.

CHAPTER LXI

THE PITUITARY GLAND (HYPOPHYSIS CEREBRI)

DEVELOPMENT AND STRUCTURE

The average weight of the human hypophysis is about 0.5 gram. Its average dimensions are $10 \times 13 \times 6$ mm., it is larger in females, especially in those who have borne children, than in males. The gland is attached to the base of the brain between the optic chiasma in front and the tuber cinereum and corpora mammillaria behind by a short stalk. The gland proper is ensconced within the small cavity formed by the sella turcica of the sphenoid which is closed above by a membrane—the *diaphragma sellae*. The latter is pierced by the pituitary stalk. Upon gross examination the pituitary is seen to consist of two parts—the *anterior* and *posterior lobes*—which can be readily separated with the fingers. These parts differ from one another developmentally, histologically and functionally.

The *anterior lobe* arises as an evagination of the ectoderm of the primitive buccal cavity. This hollow pouch (craniopharyngeal duct or pouch of Rathke) grows upwards to meet the downgrowing evagination of the floor of the 3rd ventricle which is destined to form the *pars nervosa* of the *posterior lobe*. The pressure of the hollow anterior lobe rudiment against the developing *pars nervosa* causes invagination of the posterior wall of the former and the almost complete obliteration of its cavity. A narrow cleft alone persists in the fully formed gland to represent the collapsed cavity of Rathke's pouch. It is the presence of this cleft which allows the gland to be so easily separated into two parts. These two rudimentary parts of the pituitary are dependent upon one another for their subsequent development, as is shown by the fact that neither one when grafted into an animal will grow unless it is accompanied by a fragment of the other (Blount). Though the fully formed human posterior lobe and stalk are quite solid in some animals such as the cat the cavity persists to adult life and communicates with the 3rd ventricle.

That portion of the pituitary which is derived from the posterior wall of Rathke's pouch, and is in intimate contact with the posterior lobe, but separated from the bulk of the anterior lobe by the cleft, is known as the *pars intermedia*. In animals, the latter is only 2.5 per cent of the entire gland. The portion of the gland lying in front of the *pars intermedia* and separated from it by the cleft is called the *pars anterior*. The epithelial tissue originally derived from Rathke's pouch also extends upwards and spreads over the base of the brain around the pituitary stalk. This layer of tissue, since it invests the tuber cinereum, is called the

pars tuberalis; it is considered a part of the anterior lobe. The *pars intermedia*, though from its origin should be considered a part of the anterior lobe is, account of its close association with the posterior lobe, usually included as a part of the latter. The several parts of the pituitary are shown in figure 2 and listed in the subjoined table.

Origin	From primitive buccal cavity	<div> <div>pars anterior</div> <div>pars tuberalis</div> <div>pars intermedia</div> </div>	anterior lobe
	From floor of 3rd ventricle	<div> <div>pars nervosa</div> <div>pituitary stalk</div> </div>	posterior lobe

The *pars anterior* is richly vascular, showing numerous blood sinuses between cords of cells. The cells fall into two main groups, (1) *chromophobe* or *residual* cells which possess no granules, stain lightly and apparently do not secrete, (2) *chromophil* cells which contain large numbers of granules which stain readily. They are believed to elaborate the secretion of the anterior lobe. On a basis of the character of the granules, the chromophil cells are grouped again in two varieties, (a) *acidophil* (or *alpha*) cells which stain more readily with acid dyes, and (b) *basophil* (or *beta*) cells which have a greater affinity for basic stains. The three types of cell (chromophobe and the two types of chromophil cell) are scattered indiscriminately throughout the *pars anterior*. The proportions found by Rasmussen in man, were around 50 per cent chromophobes, 35 per cent acidophils and 15 per cent basophils. The last are increased after castration (p. 756). It now appears that the chromophobes represent an early stage in the development of the granular (chromophil) cells and give rise to either acidophils or basophils. The *pars intermedia* of man often shows cysts of various sizes containing a hyaline or colloid material and a few cells filled with the same material (*hyaline bodies*). The *pars tuberalis* resembles the *pars anterior* in being constituted of cords of cells separated by blood sinuses. The cells, however, are non-granular.

The *pars nervosa*, including the *stalk*, is composed (a) neuroglial cells, (b) fusiform cells with several processes and containing granules of a brown pigment in their cytoplasm (*pituitocytes*), (c) numerous nerve fibers, and (d) hyaline bodies. The hyaline bodies were believed by Herring, Cushing and others to represent cells of the *pars intermedia* and *pars tuberalis* which have undergone a hyaline change and are traveling the *pars nervosa* and stalk to reach the 3rd ventricle.

the hyaline material with which they are filled has been thought to represent the hormone of the posterior lobe. Some doubt has been thrown upon this view and many consider these bodies simply as artefacts.

Wislocki and King have investigated the blood supply of the hypophysis of the monkey and of man. The following description is based upon their observations. Except for a few capillary anastomoses, the blood supply of the pituitary is independent of that of the brain proper. It is derived from the hypophyseal arteries, branches of the internal carotid. The circulation of the pars anterior and pituitary stalk is also separate from that of the pars nervosa. The stalk receives its blood supply from the superior hypophyseal arteries which form a rich plexus surrounding it and covering the pars tuberalis. Blood from the stalk drains into venules tributary to the plexus. As pointed out a few years ago by Popa and Fielding the general plan of the circulation of the pars anterior resembles that of the liver. Portal venules arising from the

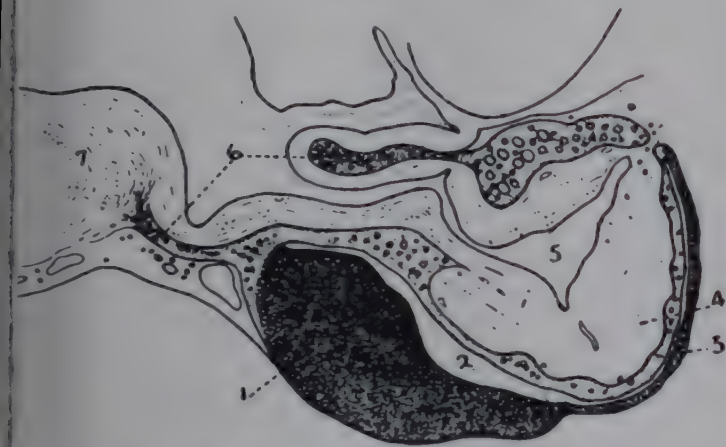


FIG. 284. Hypophysis of cat. 1, pars anterior; 2, hypophysial cleft; 3, pars intermedia; 4, pars nervosa; 5, infundibular cavity; 6, pars tuberalis, and 7, optic chiasm. (From Cowdray, redrawn after Herring.)

plexus surrounding the pituitary stalk terminate in the sinusoids of the pars anterior. The sinusoids receive blood as well from branches of the superior hypophyseal arteries, and drain into the cavernous sinus. The blood supply of the pars nervosa is derived from the inferior hypophyseal arteries.

THE NERVE FIBER CONNECTIONS OF THE HYPOPHYSIS. The pituitary is supplied with fibers derived from the internal carotid nerve plexus. The cell stations of these fibers are in the superior cervical ganglion; they reach the gland along blood vessels which descend the pituitary stalk. The *posterior lobe* also receives fibers (50,000 in number according to one estimate) from the supra-optic nucleus and tuber cinereum situated in the hypothalamus. From the hypothalamic nuclei a few fibers have been traced into the pars intermedia and fewer still for a short distance into the pars anterior. (See fig. 374, p. 1486.) The secretory activity of the pituitary can be aroused by stimulation of the cervical sympathetic.

THE PHYSIOLOGY OF THE PITUITARY

THE ANTERIOR LOBE

The anterior lobe of the pituitary is the master gland of the endocrine system. At least eleven types of physiological effect have been identified with this part of the pituitary. Six of these, since they can be produced each by an extract relatively free from other effects, are generally attributed to distinct and separate hormones, namely, (1) the *growth* hormone, (2) the *thyrotropic* (or *thyrotrophic*)¹ hormone, (3) the *adrenocorticotrophic* (or *adrenocorticotrophic*) hormone, (4) and (5) the *gonadotropic* (or *gonadotrophic*) hormones, and (6) *prolactin* or the *lactogenic* hormone.

The remaining effects of anterior lobe extracts, but for which separate hormones have not been definitely demonstrated, are: (7) *ketogenic*, (8) *insulin antagonizing* or *glycotropic*, (9) *diabetogenic*, (10) *parathyrotrophic* and (11) *pancreatrophic*. These various actions of anterior pituitary extracts can be divided into two main groups; (a) those such as the effects upon growth, milk secretion, fat metabolism, etc., which are exerted upon peripheral tissues, and (b) those which act upon other endocrines, e.g., thyroid, adrenal cortex, gonads, etc.; these latter are given names composed in each instance of the name of the gland acted upon and the suffix *tropic*.

Though convenient and customary, it is scarcely correct to speak of these pituitary principles as hormones, for there are no means of knowing whether or not the active materials obtained by extraction of the dead pituitary, often by rather drastic methods, are secreted by the living gland. There are only three characteristic types of cell in the anterior lobe of the pituitary and the evidence points to only two—the acidophils and basophils—as elaborating physiologically active principles. It is hardly credible that the several extraction products of the anterior lobe represent true hormones secreted by these two cell types. In other words, as Riddle says, too many hormones have been

¹ The Third International Conference on the Standardization of Hormones has recommended that the suffix *-tropic* in the adjectives qualifying the hormones of the anterior pituitary be replaced by *-trophic* (See Collip), and that the termination *-trophin* be used in forming the name of the hormone (e.g. thyrotrophin for the thyrotropic hormone). The suffix *-tropic* is from the Greek *τρέπειν*, to turn, and in this sense has been used in such terms as heliotropic, geotropic etc. The suffix *-trophic* is derived from the Greek word *τροφή*, to nourish or nurture and is, therefore, more appropriate as an ending for those pituitary hormones which affect the development and growth of other endocrines.

postulated. He suggests that at the most there are probably but two true hormones, one with lactogenic, adrenotropic and growth effects secreted by the acidophil cells, and another with gonadotropic and possibly thyrotropic effects secreted by the basophils. The different products which have been obtained in nearly pure form, as judged by the predominant physiological effects which they exert, he prefers to call "hormone fragments." Collip also visualises two large hormone molecules with prosthetic groups possessing the specific physiological actions demonstrable in the various laboratory products and which represent, presumably, parts broken off or "chemically dissected" from one or other of the parent compounds. Of the principles which have been obtained from pituitary tissue only the lactogenic, follicle-stimulating and possibly the luteinizing (p. 756) have been demonstrated in the blood. Until this has been done for any particular pituitary extract it is not justifiable to conclude that it is secreted as such by the gland. The pituitary principles are protein in nature, but none has been synthesized nor has any been isolated in crystalline form, with the exception of prolactin (p. 765). Little is known of their chemical structure, although from certain investigations, it appears that the gonadotropic principles are glycoproteins containing glycosamine and a hexose which is probably mannose. It has been rather surprising to find, that unlike the thyroid hormone, insulin etc., the pituitary principles are species specific. Thus, differences in action have been shown between the pituitary hormones of sheep, pigs and cattle.

The effects of hypophysectomy are for the most part attributable to the withdrawal of the actions of the anterior lobe secretion upon various physiological functions. In competent hands complete ablation of the pituitary is not the fatal operation it was once believed to be; animals survive for long periods during which they can be studied, though undoubtedly their life span is shortened as a result of the abnormalities which result. Among the chief effects of hypophysectomy are (1) arrested growth, (2) atrophy of the gonads and, indirectly, of the accessory organs of sex, (3) suppression of milk secretion and involution of the mammary glands, (4) atrophy of the thyroid and adrenal cortex and probably degenerative changes in the parathyroids, (5) lowered metabolic rate, (6) hypoglycemia and increased sensitivity to insulin, reduction in liver and muscle glycogen, (7) depression of spontaneous activity, (8) diminished resistance to infections and shock.

The growth hormone

It has been known for many years as a result of the study of growth abnormalities in man

(acromegaly, gigantism and dwarfism) that the anterior lobe of the hypophysis influences skeletal growth. Experimental work also indicated such a function, removal of the posterior lobe and part of the anterior from puppies resulting in dwarfing, sexual infantilism and obesity (Aschner, Cushing). Removal of the anterior lobe in tadpoles was shown by Smith and by All to result in retarded growth, failure of metamorphosis and a reduction in pigmentation of the body surface. The final proof that the anterior lobe secreted a growth-promoting hormone was furnished by the experiments of Evans and Long

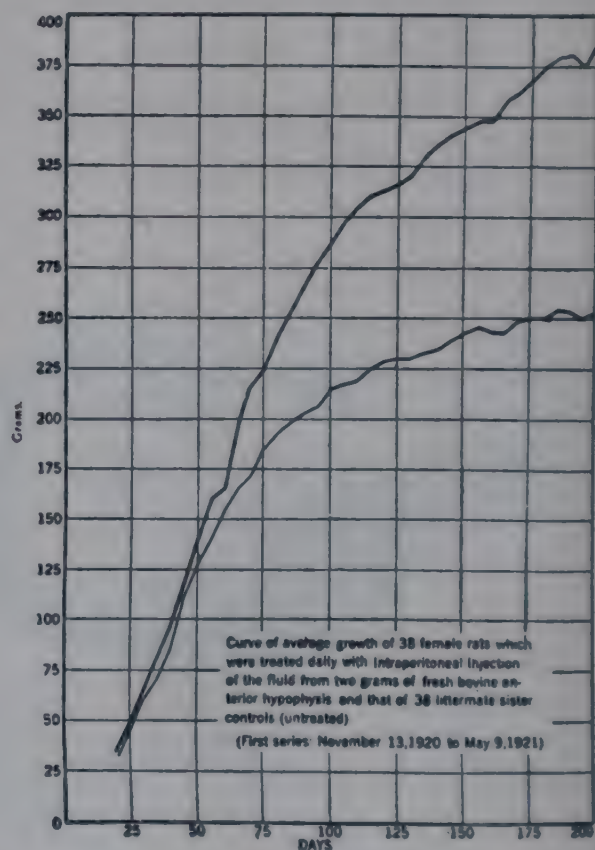


FIG. 285. Curve of average growth of 38 female rats which were treated daily with intraperitoneal injection of anterior lobe extract, and that of 38 littermate sister controls (untreated). (After Evans.)

who found that a saline or alkaline extract of the gland when given daily to rats by intraperitoneal injection (but not by mouth) extended the growth period beyond the normal limit. Some of these animals finally attained a size larger by 10 per cent or more than that of their untreated littermates (see fig. 285). The effect was usually greater in females. Similar results have been obtained in dogs. Gigantism, acromegaly and splanchnomegaly (p. 737) have been produced in bulldogs by Putnam, Benedict and Teel. Air dales, Boston terriers and dachshunds have been shown by others to respond to such an extract (see fig. 286). Potent extracts free from gonadotropic and containing only traces of thyrotropic, adrenotropic and lactogenic principles have been

prepared.² As might be expected, the stimulus to growth is accompanied by a retention of nitrogen. An increase in deposit protein appears to be one of the first changes in protein metabolism caused by the growth principle. There is no appreciable change, however, in the calcium balance. The growth principle is almost certainly elaborated by the acidophil cells. The pituitaries of dwarf mice are lacking in acidophils while acromegaly and gigantism are frequently associated with tumors composed of these elements.

It might with reason be asked, "Does the growth principle act indirectly by stimulating other glands which are known to be influenced by the pituitary, e.g., the thyroid, adrenals or gonads?" Such an indirect mode of action is disproved by the fact that growth cannot be induced in an hypophysectomized animal by the administration of an extract of any of these glands. On the other hand, growth can be induced in hypophysectomized animals or stimulated in young normal animals by means of pituitary extracts containing only traces of "tropic" principles. The growth hormone should not, however, be looked upon as the

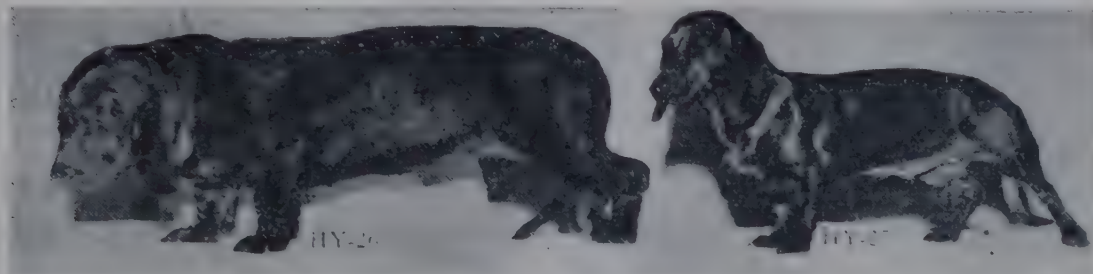


FIG. 286. Litter mate female dachshunds 11½ months old. HY-26 injected with growth hormone for 35 weeks HY-27 control. (After Evans and associates.)

Diabetogenic and ketogenic effects are associated with the growth hormone and cannot be completely separated from it. The growth hormone exhibits other metabolic effects, namely, depression of the respiratory quotient, a decrease in arginase of the liver and of insulin in the pancreas. Also, the specific dynamic action of protein appears to be dependent upon this principle. It is not known whether these various metabolic effects are essentially and specifically related to the growth hormone or are due to separate and distinct principles.

The effect of hypophysectomy upon the growth of puppies is shown in fig. 287. The potency of a given anterior lobe extract in growth-promoting properties may be assayed by injecting it in measured amounts into rats whose growth has been completely arrested by subjecting them to hypophysectomy at the age of 100 days and thereafter following their growth curves. Normal rats are much less reactive to the hormone than the operated animals.

The pituitary of a full-grown animal contains as much growth hormone as those of young animals, but the rôle which it plays in the adult body is unknown. It may be mentioned, however, as an isolated observation that under its influence the growth of hair over a shaved part is more rapid than usual.

² Riddle and his associates doubt that a specific growth hormone exists; they believe that the growth effect is the result of the combined actions of prolactin and thyrotropin.



FIG. 287. Hypophysectomized puppy (right) and litter-mate control (left) three months after removal of the hypophysis when three weeks old. (After Dandy and Rickert.)

supreme factor controlling growth in the sense that cell multiplication and the growth of tissues and organs are arrested when it is withdrawn. That the growth of individual organs is not abolished is shown by the facts that in the absence of the pituitary mitotic figures appear in the mammary glands of parturient rats, and, hypertrophy of the remaining kidney follows unilateral nephrectomy. The pituitary appears to preside over the growth of the body as a whole and to control the proportional growth of the several organs and parts.

The thyrotropic (or thyrotrophic) hormone— thyrotropin (or thyrotrophin)

Hypophysectomy causes atrophy of the thyroid.³ On the other hand, an acid extract of the anterior

³ The thyroid exerts in turn an influence upon the pituitary as indicated by the fact that thyroidectomy is followed by hypertrophy of the pars anterior with degeneration of the basophil cells and disappearance

lobe of the pituitary has been prepared (Loeb and Bassett; Aron) which, when injected into animals, stimulates the thyroid. A homogeneous substance with a high thyrotropic activity, and which appears to be a pure protein (a pseudoglobulin), has been isolated more recently from beef pituitary tissue. It is free from growth and gonad-stimulating properties. Striking changes in the histological appearance of the thyroid result from the injection of thyrotropin; the colloid material disappears, the epithelium becomes hyperplastic and the alveolar cavities collapse (fig. 288). Mitotic figures (especially after the administration of colchicine (p. 766) appear in the thyroid in large numbers; whereas in the normal gland of the guinea-pig about 150 mitoses can be found, nearly 200,000 may appear after the administration of a potent thyrotropic principle. Signs of hyperthyroidism, e.g., increase in heart rate, rise in metabolic rate, increased susceptibility to oxygen want and increased tolerance to acetonitrile have been observed by various workers. It decreases the iodine content of the gland in normal animals while raising that of the blood. The iodine intake exerts an important effect upon the action of the hormone, a fact which has an important bearing upon the mode of action of iodine in the treatment of Graves' disease. It was found by Anderson and Evans in experiments on rats that at certain levels of dietary iodine the thyrotropic principle, while it induced thyroid hyperplasia in the usual way, did not raise the metabolic rate. In other words, iodine appears to prevent the release of the thyroid hormone without preventing the action of the thyrotropic principle from exerting its usual effect upon the thyroid cells.

Thyrotropin has been demonstrated in normal blood and urine. Its concentration in the blood is increased in acromegaly and hyperthyroidism, but reduced in Simmond's disease (see also p. 738).

The thyrotropic hormone induces creatinuria and increased calcium excretion, and a reduction of liver glycogen in ordinary laboratory animals, and hastens the metamorphosis of tadpoles—all well known thyroid effects. None of the effects so far listed can be produced after removal of the thyroid.

of the acidophils. The administration of thyroxine causes a reduction in number of the granules in the acidophil cells. According to Evans the growth-promoting function of the pituitary is dependent upon a normally functioning thyroid. He states that thyroidless tadpoles can be induced to metamorphose or cretin dwarfs to grow by either the administration of thyroid, which stimulates the hypophysis, or by treatment with the pituitary growth hormone itself.

Thyrotropin causes exophthalmos in the guinea-pig, either in the normal or thyroidectomized animal (p. 677) and prevents atrophy of thyroid in hypophysectomized rats. Its action has been demonstrated in man, injections causing a rise in the metabolic rate in normal persons, hyperthyroid patients and those suffering from pituitary deficiency, but not in subjects of hypothyroidism. *In vitro*, this hormone causes hyperplasia of sliced thyroid tissue, evidence that its action is directly upon the thyroid cells. A pure thyrotropic hormone has been obtained free from the growth and gonad-stimulating principles, not free from traces of the adrenotropic principle. The normal rat, after an initial response period during which hyperplasia of the thyroid and a rise in metabolic rate occur, becomes refractory to thyrotropic hormone. The refractoriness has been shown by Collip and Anderson to be due to the formation of an inhibiting substance (a hormone (see p. 729)) which they have found in the serum of the treated animals. Friedgood has found that though guinea pigs responded at first to anterior pituitary extract by thyroid hyperplasia and a rise in the basal metabolic rate, the animals later became refractory. The responsive period was followed by one during which the B.M.R. returned to normal or to a subnormal level (though injections were continued); the thyroid hyperplasia, however, persisted. Eventually the thyroid returned to its normal size and histological appearance, in spite of the uninterrupted administration of the extract. Slight prominence of eyeballs appeared toward the end of the responsive phase, but the most pronounced exophthalmos occurred during the refractory phase. The production of the effect upon the eyes appears therefore, to be independent of the effect upon B.M.R. It has been mentioned elsewhere that exophthalmos has been induced by administration of anterior pituitary extract in thyroidectomized animals.

The discovery of the thyrotropic hormone and the observations just cited suggest at once the possibility that exophthalmic goiter and certain instances of hypothyroidism are primarily of pituitary origin—excess and deficiency, respectively, of the thyrotropic principle.

The adrenocorticotrophic (or adrenocorticotrophic) hormone—corticotropin (or corticotrophin)

Hypophysectomy in the rat leads to atrophy of the cortex of the adrenal (fig. 289). Hypertrophy of the adrenals (cortex and medulla) is

erved by Cushing and Davidoff in hyperactivity of the anterior pituitary in man (see hypomegaly and pituitary basophilism, p. 737); whereas pituitary cachexia (p. 738) is associated with adrenal atrophy. Adenomatous tumors of the adrenal cortex have been produced by the injection of anterior pituitary extracts into normal animals. Some cases of Addison's disease, it has been suggested, may be due to a pituitary defect, that is, to a deficiency of corticotropin; improvement of patients with this disease has been reported to follow the administration of the adrenocorticotrophic principle.

Collip and his colleagues (1933) were the first to prepare from the anterior pituitary an extract which acted specifically upon the adrenal cortex; it contained minimal amounts of other pituitary principles. This extract was highly effective in restoring to normal the atrophied adrenal cortex of

the production of those cortical principles possessing an oxygen atom at C_{11} . The production of those hormones lacking an oxygen atom at C_{11} does not appear to be stimulated by this pituitary principle.

The basophil cells are probably the source of corticotropin. A great reduction in the number of these cells is said to occur in some cases of Addison's disease.

The gonadotropic hormones and prolactin are dealt with in Chapter LXII.

The ketogenic effect

If an extract of the anterior lobe be injected into fasting rats, or rats receiving a diet of butter fat, a rise in acetone bodies in the urine and in the blood occurs (Burn and Ling, Anselmino and Hoffmann). The effect is not mediated through the thyroid for it is obtained in thyroidectomized

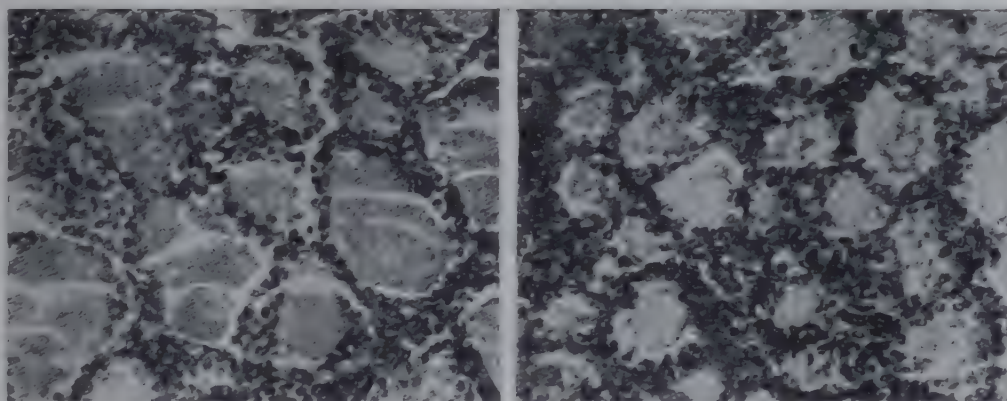


FIG. 288. The thyrotrophic hormone. Section of thyroid from normal guinea-pig on the left, that of litter mate treated with 8 mg. of anterior lobe substance on right. (After Van Dyke, *The physiology and pharmacology of the pituitary body*, Chicago University Press.)

hypophysectomized animals. A pure protein with high corticotropic activity was isolated by Li and associates in 1942, and by Sayers and his colleagues in 1943. The material obtained by the latter observers is free from thyrotropic and ketogenic actions. Its isoelectric point is at a pH between 4.7 and 4.8 and its molecular weight is around 20,000. It has a definite corticotropic action in daily doses of micrograms.

Corticotropin induces changes in the quantity and distribution of the doubly refracting (birefringent) lipid material in the cortical cells. Moderate doses cause a reduction of the fine granular particles. With larger doses the lipid is increased in the zona glomerulosa and zona fascicularis and appears in the form of larger accumulations which, it is suggested by some observers, represent the cortical hormone or its precursor in the storage phase (p. 684). Gratten and Jensen found that corticotropin stimulated

animals. It was thought, however, to be dependent upon the adrenal cortex since adrenalectomized animals treated with a potent ketogenic extract do not show ketonuria (Fry), whereas removal of the adrenal medulla alone does not prevent the response. It has been found, however, that the effect of the adrenal cortex is only upon the excretion of ketone bodies; adrenalectomy does not prevent their rising in the blood. Ketogenic extracts also cause an increased deposition of fat in the liver and a diminution of body fat, indicating the transference of fat from the latter to the former site, which suggests in turn that the ketosis is the result of the stimulation of fat catabolism, and the production of ketones beyond the capacity of the body to oxidize them. The ketogenic effect is closely associated with the growth hormone and the diabetogenic factor (see below). Animals develop a resistance to the action of ketogenic extracts after they have

received a number of injections (see *antihormones*, p. 729).

The insulin-antagonizing (glycotropic or glycotrophic) and diabetogenic factors
(see also p. 589)

Many observations associate the anterior lobe of the pituitary with carbohydrate metabolism. (a) Hyperglycemia, glycosuria, lowered sugar tolerance, are among the effects of overactivity of the anterior lobe in man (see acromegaly, p. 736). All the symptoms of a true diabetes mellitus may be present in this condition. (b) Evans and others observed the dachshund pups given daily injections of anterior lobe extract as

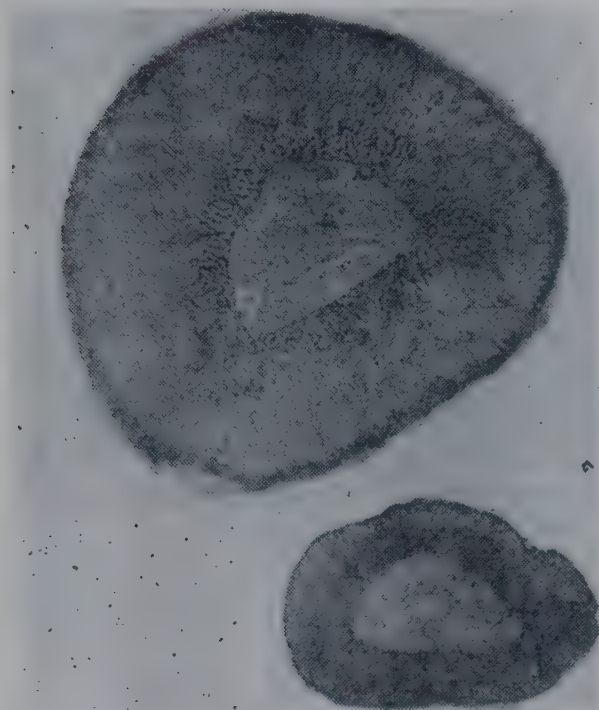


FIG. 289. Showing adrenal atrophy following hypophysectomy. Normal gland on left, gland of hypophysectomized animal on right. (After P. Smith.)

well as increasing 100 per cent in weight, exhibited great thirst, polyuria and glycosuria, and had a fasting blood sugar of 232 mg. per 100 cc. (normal 100 mg. per cent). (c) Hypophysectomy renders an animal hypersensitive to insulin and resistant to the hyperglycemic action of adrenaline, while implantations of anterior lobe or injections of an anterior lobe extract reduces the hypoglycemic action of the pancreatic hormone. It was also shown by Houssay that the diabetic symptoms following pancreatectomy almost disappear after hypophysectomy, but return when anterior lobe tissue is transplanted into the depancreatized and hypophysectomized animal. A pancreatectomized and hypophysectomized dog (Houssay dog) will live for several months without the aid of insulin;

during fasting the blood sugar is within normal limits, or there may be hypoglycemia; ketonuria is absent and the glycogen content of the liver is near the normal value. Houssay and Best conclude that the anterior lobe is concerned in the production of sugar from endogenous sources (see also p. 544). Corkill, Marks and Best suggested that the glycogen reserves of the liver are less readily mobilized after hypophysectomy and that this is a contributory factor in the hypersensitiveness to insulin of animals subjected to this operation. The hyperglycemic effect of anterior lobe extracts is not brought about through the adrenal since it occurs after adrenalectomy (Houssay).

In 1937 Young reported the extremely important finding that dogs given a series of daily injections of a crude extract of the anterior lobe became *permanently* diabetic (hyperglycemia, glycosuria and ketonuria), i.e., the diabetogenic effect continued after the administration of the extract was stopped, and persisted indefinitely. The pancreases of such animals show complete degeneration of the islets of Langerhans (Richardson and Young) and give an extremely low insulin response (Best and Campbell). These changes probably represent an "exhaustion atrophy" which accounts for the permanent diabetic state induced by the extract. The diabetogenic factor should not be confused with the insulin-antagonizing principle, or, as Young calls it, the glycotropic factor. The latter exerts a true anti-insulin effect. Experiments have been secured, for example, which, by reducing or preventing the hypoglycemic action of injected insulin, do not raise the blood sugar when administered alone. The glycotropic factor, which is distinct from the thyrotropic and gonadotropic principles and probably from the lactogenic factor, also inhibits the actions of insulin in accelerating the fall in blood sugar in hepatectomized animals (Himsworth and Scott) and in preventing the deposition of muscle glycogen (Marshall).

The parathyrotropic (or parathyrotrophic) factor

There is a considerable body of evidence which suggests that the anterior lobe exerts a controlling influence upon parathyroid function. The occurrence in the human subject of parathyroid adenomas with pituitary tumors has been reported. Decalcification of the skeleton occurs in pituitary basophilism (p. 737), though in a case of this disease Cushing found degeneration rather than hyperplasia of parathyroid tissue. Atrophy of the parathyroids has been reported in dogs

y and associates) and in rats (Smith) following hypophysectomy. Collip and his colleagues observed hypocalcemia and degenerative changes in the parathyroids in dogs after the removal of the pancreas and the hypophysis. Removal of the pituitary alone, however, does not lower the serum calcium, though a rise in serum calcium has been observed to result from injections of anterior pituitary extracts. Anselmino and Hoffmann claim to have produced parathyroid hyperplasia, often accompanied by hypercalcemia, by the injection of an anterior lobe extract into animals, and to postulate the existence of a specific parathyrotropic hormone. Similar results have been reported by Hertz and Kranes. Finally, Hertz and Albright have reported that the urine of a subject in whom there was a general hyperplasia of parathyroid tissue (hyperparathyroidism, p. 708), when injected into rabbits caused hyperplasia of their parathyroids. Although these several observations suggest some relationship between the pituitary and parathyroid function, there is no conclusive evidence that a specific parathyrotropic hormone exists; and that such a hormone is essential for parathyroid function is disproved by the fact that calcium metabolism, even in young animals, appears to suffer no impairment after hypophysectomy.

The pancreatic (or pancreatrophic) effect

Anselmino and Hoffmann reported the preparation of an anterior lobe extract which caused enlargement and an increase in the number of the islets of Langerhans together with a fall in blood sugar. The extract was free from thyrotropic effects. Their results, they believed, indicated the presence of a pancreatic hormone which stimulated insulin production. Richardson and Young have furnished confirmatory evidence of a pancreatic effect. They observed a 100 per cent increase in the quantity of islet tissue in the pancreases of rats receiving daily injections of a crude anterior lobe extract; many mitotic figures were seen in the islet cells of dogs treated with the extract. Marks and Young found that in rats the administration of a pituitary extract increased the insulin content of the pancreas. Ham and Haist have obtained histological evidence of a stimulating effect of a pituitary extract upon the islet and acinar tissue. After a few daily injections mitotic figures appeared in the beta cells of the islets as well as in the acinar cells. Signs of increased activity were also observed in the thyroid and adrenal cortex. The daily adminis-

tration of extract over a longer period led to degranulation followed by hydropic degeneration of the beta cells and, eventually, atrophy of the insulin-secreting tissue.

The pancreatic effects of pituitary extracts which have been just cited do not permit one to conclude that a specific pancreatotrophic hormone exists. Such effects more probably are brought about indirectly through the action of the diabetogenic or of the glycotrophic factor, that is, by increasing the demand for insulin. The fact that hypophysectomy is not followed by atrophy of the islets of Langerhans speaks very strongly against the effects being truly "tropic" in character.

ANTIHORMONES

Collip and his colleagues have demonstrated that certain hormones when injected cause the formation of a substance in the serum of the treated animal which exerts a specific antagonism to, and may completely abolish the effect of, the injected hormone. They claimed that the inhibitory principle was not an antibody in the ordinary sense, i.e., an immune body developed to some constituent of the hormone acting as antigen, but was rather in the nature of an *antihormone*. A substance of this character was first obtained by Collip and Anderson in 1934 in the course of experiments with the thyrotropic principle of the anterior pituitary. Rats after repeated injections of the thyrotropic hormone became refractory (p. 726), subsequently failing to respond to large doses. They were still responsive, however, to the thyroid hormone. It was found that the serum of these refractory animals was capable of preventing the effect of the thyrotropic hormone upon non-refractory animals. There is also evidence that the pituitary produces a substance (possibly paraxanthine) which antagonizes the thyroid hormone itself; an extract of the hypophyses of rats fed desiccated thyroid tissue reduces the metabolic rate of normal animals.⁴ To give another example of this antagonism: hypophysectomized rats treated with purified growth hormone fail to respond to it after a period of five or six weeks. The serum of such animals

⁴ Paraxanthine (1:7-dimethylxanthine) is an antithyroid substance which has been isolated by Carter and his associates from animal tissues and from human urine. In suitable dosage it antagonizes the action of thyroxine, lowering the metabolic rate and slowing the isolated frog heart. It is suggested that its presence in the body may be of physiological significance, the level of the metabolic rate being due not to thyroid action alone but also dependent upon the balance between it and the action of paraxanthine.

neutralizes the effect of the growth hormone upon other untreated hypophysectomized rats. Besides anti-thyrotropic and anti-growth principles, inhibitory substances have been shown to exist for the ketogenic, lactogenic and gonadotropic principles of the anterior pituitary, respectively, as well as for the anterior-pituitary-like principle (A.P.L.), but not for the adrenotropic, or parathyrotropic principles, or for insulin, or the sex hormones.

Collip suggested that the inhibitory principles or antihormones were present in the blood of normal animals, each serving to "oppose" or "buffer" the action of the corresponding hormone and that a given endocrine effect occurring naturally in the body was dependent upon the ratio existing between the hormone and antihormone concentrations. Disordered endocrine function whether in the direction of hyper- or hypoactivity might be, according to this conception, the result of an imbalance between the two antagonistic principles, rather than of an abnormal concentration of the hormonal principle alone. In other words, an endocrine deficiency might be due to too little of the hormone or to an excess of its antihormone; a hyper-endocrine state would be the result of a reverse relationship between these two principles.

Collip's observations have been confirmed repeatedly by other experimenters, so that the production of substances antagonistic to certain pituitary principles is a phenomenon established beyond all doubt. But there is a difference of opinion as to the nature of the inhibitory substances. The problem is one of extraordinary complexity for experimental investigation. Various workers have tried to answer the question whether the effect is due to antibodies, in the immunological sense of the term, produced by a foreign protein (antigen) closely associated with the active (hormone) principle, or to a substance—a true antihormone—which directly opposes the physiological action of the particular hormone itself. The demonstration that the effect was species specific would establish it as being in the nature of an antibody reaction. Evidence on this point, however, is conflicting. Collip found, for example, that a gonadotropic extract of sheep's pituitaries when injected into lambs caused the production in their sera of an antigonadotropic substance which antagonized gonadotropic extracts prepared from the pituitaries of hogs and cattle. The antigonadotropic serum when injected into rats inhibited the gonadotropic activity of their own pituitaries. These experiments afford strong evidence against the hormone inhibitor being an antibody. Rowlands and Parkes found also that a gonadotropic extract from ox pituitaries, upon injection into rabbits, caused the formation in their sera of a substance which protected other rabbits from the gonadotropic action, not only of the original (antigenic)

extract, but of extracts from sheep and horse pituitaries. Furthermore, the antigonadotropic serum given rabbits immediately after mating inhibited ovulation which normally would have occurred about 10 hours later (p. 756). In other words, the antagonist developed against ox gonadotropic principle inhibited the gonadotropic (ovulation) principle of the recipient animal's own pituitary. Also, the transplantation of rat's pituitary tissue into rats results in the production of inhibiting substances, in this instance there can be no question of a foreign protein exerting an antigenic effect. Finally, an antithyrotropic substance has been found in the blood of normal animals (dog, sheep, rabbit and man). On the other hand, in parabiosis experiments (p. 757), in which a hypophysectomized female rat is joined to a castrate, the gonads of the former are subjected to continuous stimulation by the pituitary of the latter; that is, a substance inhibitory to the gonadotropic principle of the pituitary is not produced under these circumstances. The substances are associated with the globulin fraction of the serum, a fact which argues for their belonging to the group of immune bodies. Their source is definitely known, but at any rate the antithyrotropic substance is not formed in the thyroid, for when thyrotropic hormone is added to fluid perfusing a surviving thyroid gland, there is no indication of formation of an antagonizing substance. Nor are they produced by the pituitary itself, for the effect is actually greater in hypophysectomized than in normal animals. There is some evidence that the spleen and other parts of the reticulo-endothelial system are concerned in their production. If this can be established it will be another point in favor of these substances being antibodies. In summary, it may be stated that the evidence perhaps weighs against the antihormone theory, but it would be unwise to form a definite opinion upon this perplexing question. It may be added, however, that the failure to find an answer has not been due to any lack of experimental ardor or ingenuity.

THE POSTERIOR LOBE

An active extract of the pituitary was first obtained in 1894 by Oliver and Schafer; its effect in raising the blood pressure was described. However, three years later showed that the posterior lobe alone contained the pressor principle. This extract has been used in medicine for several years under such commercial names as *Pituitrin*, *Infundin*, etc. or as a solution of the *Standard Pituitary powder* of the U.S.P. Much of our knowledge concerning the pharmacological and physiological actions of the principle of the posterior lobe has been gained from experiments with this relatively crude material and although it has been largely displaced by the more purified fractions *pit-*

and *pitocin* (p. 733) an account of its actions will first be given.

The Actions of a Solution of Standard Pituitary Powder or of a Commercial Pituitary Extract

These fall into 5 main groups.

(1) **CIRCULATORY.** The blood pressure is raised, the systemic arterioles and capillaries both undergoing constriction. Marked pallor of the skin results. An initial depressor effect, or a pressor succeeded by a depressor effect may precede the main rise in blood pressure. A second injection of the extract shortly after the first usually causes a depression of the blood pressure (*inversion effect*). Pituitrin causes constriction of the coronary and pulmonary vessels but dilates the cerebral and renal vessels. The dilator effect upon the two last mentioned sets of vessels is a passive one being caused by the rise in systemic blood pressure. The heart is slowed by pituitrin if the vagus nerves are intact, the effect being a reflex result of the blood pressure rise, but increased cardiac rate occurs if the nerves have first been cut. Some dilatation of the heart and weakening of its beat occur in the dog, rabbit and, with large doses, in the cat. The coronary constriction and the weakening effect upon the cardiac muscle cause a reduced cardiac output and a fall in pressure in the pulmonary artery (dog and rabbit). These experimental results indicate that commercial pituitrin is of no value *clinically* as a means of strengthening the action of a failing heart but may actually exert a deleterious effect. The fall in blood pressure which follows repeated injections of pituitrin (*inversion effect*) is due, according to Melville and Stehl, to the weakening of the heart and not of vascular origin. The portal venous pressure is reduced by pituitrin—as a result of constriction of the splanchnic vessels.

(2) **PLAIN MUSCLE** is stimulated by pituitrin. This action differs from the smooth muscle stimulating action of adrenaline in that it does not parallel the action of the sympathetic nerves; smooth muscle, receiving motor innervation from the parasympathetic, is excited as well. The muscular walls of the *uterus* (*oxytotic effect*), *intestine*, *gall-bladder*, *ureter* and *urinary bladder* (detrusor and trigone) are excited. Sometimes the smooth muscle of the bronchioles is stimulated, but this is due to contamination of the extract with histamine and is not specific. The stimulating effect of pituitrin upon the isolated virgin guinea-pig's uterus was demonstrated by Dale in 1909; it is used as a means of assaying the potency

of pituitary extracts. Some highly purified preparations exert an oxytotic effect in a dilution of 1 part in 2,000,000,000. The effect of pituitrin upon the uterine muscle is antagonized by the hormone of the corpus luteum (see p. 750). The oxytotic effect varies with the species, and, as a consequence of the interplay of other hormones, especially of the luteal hormone, with the phases of the sexual cycle (e.g., period of oestrus, pregnant or non-pregnant state of the uterus). An interrelation between the actions of adrenaline and pituitrin is indicated by the fact that if the non-pregnant uterus of the cat is first treated with pituitrin, adrenaline causes contraction instead of the usual relaxation (p. 687). The human uterus is most sensitive to the extract at the end of pregnancy, and pituitrin is used as an obstetric aid to induce uterine contraction after the expulsion of the placenta and so to prevent or check post-partum hemorrhage. The posterior pituitary principle also causes a temporary increase in the secretion of milk in lactating animals (so-called *galactagogue action*). This is not, however, a specific secretory effect but is due simply to the stimulation of smooth muscle in the walls of the mammary alveoli and ducts, and the expression of pre-formed milk (p. 768).

(3) **ANTIDIURETIC EFFECT.** This was discovered by Magnus and Schafer in 1901. In the conscious animal the injection of pituitrin may cause a very brief increase in the urinary flow due to the rise in general blood pressure and the passive dilatation, thereby, of the renal vessels. The important and specific renal effect is, however, an increase in the reabsorption of water and, as a consequence, a reduction in the urinary flow. In anesthetized animals the specific antidiuretic action is absent; diuresis due to the vascular factors is the outstanding effect. Pituitrin postpones for several hours the diuresis induced in normal animals by water drinking, and reduces the polyuria of diabetes insipidus. Associated with the antidiuretic effect is an increase in the percentage of chloride in the urine and, as a result of a reduction in the tubular reabsorption of chloride, an increase in the total amount excreted (pp. 385, 386 and 398). The antidiuretic principle is an essential factor in the maintenance of the water balance of the body, being secreted when the need for water conservation arises. For example, the quantity of the hormone in the urine, which reflects presumably its concentration in the blood stream, is increased in dehydrated states but decreased in hydremia (Gilman and Goodman).

(4) **METABOLIC EFFECTS.** Reduced tolerance for sugar, diminution in hepatic glycogen, hyperglycemia, glycosuria and a fall in the basal metabolic rate follow the injection of pituitrin. The effect of insulin is antagonized. That is, to say, the pancreatic hormone produces less effect upon the blood sugar and a greater amount is required to produce hypoglycemic convulsions if its administration has been preceded by an injection of pituitrin. Pituitrin also causes an increase in liver fat.

Geiling and DeLawder found that after the injection of pituitrin (or pitressin, p. 733) the muscles for a short time pass into a state suggesting that their activity was being carried on under anaerobic conditions. The blood issuing from the muscles was arterial in color, it had a low content of CO_2 and a high content of O_2 , glucose, lactic acid and inorganic phosphorus. The cardiac output and the total oxygen consumption fell. This phase was followed by one in which the conditions were reversed, the blood being more venous than usual. The cardiac output and the total oxygen consumption rose. The mechanism whereby these effects are produced, whether primarily metabolic or vascular in nature, is unknown.

(5) **MELANOPHORE-EXPANDING (-DISPERSING) PROPERTY.** In the skins of many cold-blooded animals are peculiar cells with branching processes and containing mobile pigment granules whose movement toward the periphery of the cell or toward the center is under hormonal influence. Such cells have been given the general name of *chromophores*. Those containing black pigment (melanin) are known as *melanophores* and those with red or yellow pigment are called *erythrophores* or *xanthophores*, respectively.

Hogben and Winton showed that pituitrin caused the pigment granules in the melanophores of the frog to become dispersed throughout the bodies and branching processes of these cells. This results in darkening of the skin. Thus, the injection of a drop or so of a solution of pituitrin into a frog causes its skin to become almost coal black as a result of the melanophore reaction. On the other hand, after hypophysectomy, owing to the disappearance of the pituitary hormone from the circulation, the pigment granules gather near the center of the cells and the skin becomes pale. Hypophysectomized tadpoles have, instead of the usual dark-brown or green color, a silvery appearance. The changes in color which certain amphibia, reptiles and fish undergo in

order to blend into the color of their surroundings is largely due to variations in the concentration of the pituitary hormone in the blood or to the balance between the concentrations of melanophore-expanding principle and adrenaline. Blinding frog deprives it of this adaptive power.⁵ Nerve impulses arising in the retina are believed, therefore, to govern the liberation of the melanophore-expanding principle. The production of melanin in the skin of the frog is said to be stimulated by this principle. It has also been found to accelerate *in vitro* oxidation of the tyrosine-tyrosinase system (p. 685).

In most animals, the melanophore-expanding principle is elaborated by the pars intermedia. Cultures of tissue from the pars intermedia also yield this principle, whereas, cultures of the neural part of the pituitary or of the anterior lobe do not. Nevertheless, the principle finds its way into the neural part of the pituitary and unpurified extracts of the latter always contain it as a contaminant. But it is possible to prepare it free from antidiuretic, pressor and oxytocic effects. Moreover, the melanophore dispersing action of extracts from different parts of the posterior lobe do not run parallel with the pressor, oxytocic and antidiuretic

⁵ The phenomenon of light influencing structure and function through the mediation of a retinohypophyseal mechanism is not peculiar to cold-blooded animals. The work of a number of experimenters indicates that the well known association of the seasonal periods with morphological changes (e.g., color and texture of hair or plumage) and with the sexual cycles of certain mammals and birds as well as with the migration of birds, is due, in part at least, to light acting upon the anterior pituitary through the medium of retinal impulses. Rowan, for example, was able to induce sexual activity in crows and canaries at any desired time of the year by varying the periods of their exposure to artificial light; it is also well known that the domestic fowl will lay regularly in winter if its period of exposure to light is lengthened by artificial means. Cognitive experiments have been carried out upon mammals: ferrets, hedgehogs and raccoons. The seasonal shedding of hair in the ferret has been shown to be conditioned by the length of the day; and optic nerve section or hypophysectomy abolishes the phenomenon. The sexual cycles are abolished, of course, by hypophysectomy (lack of gonadotropic hormone) but their periodicity in relation to the length of exposure to light is lost after optic nerve section alone. The extreme sensitivity to light of the pigeon in respect to the time of egg laying is extraordinary. The pigeon lays a pair of eggs in the morning, the second of the pair being laid with the regularity of clock-work half an hour after the first. Lengthening or shortening the period of exposure to light alters the duration of the interval between laying of the first and second eggs of the pair.

⁶ In those species such as the chicken, porpoise and whale which do not possess a pars intermedia, the melanophore-dispersing principle is found in extracts of the anterior lobe; none is present in the posterior lobe.

diuretic properties. These facts argue for the melanophore effect being due to a separate and distinct hormone. Zondek has given the name *intermedin* or the *chromatophorotropic hormone* to this principle. It has been suggested that the melanophore-expanding principle also causes the migration of the melanin granules in the pigment layer of the retina (p. 956) and is, therefore, a factor in dark adaption of the eyes of higher vertebrates, but the experimental evidence in respect to such a function is conflicting. Nor is there any definite evidence that any relationship exists between this hormone and the occurrence of retinitis pigmentosa (p. 742). It is natural that it should also be suspected of playing a rôle in cutaneous pigmentation in the human subject but again no reliable observation has been reported which might connect this principle with either normal or abnormal pigmentation in man.

Fractionation of the posterior lobe extract. Pitocin and pitressin

Considerable quantities of histamine may be present in commercial pituitary extracts which have not been carefully purified; indeed it was believed for a time by some (Abel and associates) that the plain muscle stimulating and depressor effects were due simply to histamine. Abel also maintained that the other effects (pressor and antidiuretic) were due to a single hormone. The work of Dudley, and especially of Kamm and his associates has shown that the specific effects are not due to histamine, and that there are at least two distinct active principles in a posterior lobe extract. From the crude extract Kamm and his associates have isolated two relatively pure fractions which are called, respectively, *pitocin* and *pitressin*. These are white amorphous powders freely soluble in water. Chemical analyses of highly purified preparations have revealed a high amino-acid content of both pitocin and pitressin; cystine, tyrosine and arginine are found in greatest amounts. Pitocin is the uterine-stimulating (oxytocic) principle and is 100 to 350 times more potent in this regard than the solution of Standard Pituitary Powder.⁷ It acts upon the

muscle of the uterine body but not upon that of the cervix. Pitressin is responsible for the vascular, intestinal-stimulating and antidiuretic effects. If a series of injections of pitressin be given at short intervals a certain degree of tolerance becomes established, the hypertensive effect being less with successive doses. Not uncommonly an initial fall in blood pressure preceding the pressor effect of a single injection occurs; this is attributed to a temporary sharp reduction in cardiac output due to coronary constriction. It is possible that the antidiuretic action of preparations of pitressin is due to a separate principle, for the pressor effect is more readily destroyed by heat than is the antidiuretic action. Preparations of pitressin with a pressor activity 300 times greater than that of a solution of Standard Pituitary Powder have been prepared.

Pitocin exerts its greatest effect upon the human uterus in the later months of pregnancy. In the first few months this principle exerts no oxytocic action, but a slight effect upon the uterus, probably of vascular origin follows the injection of pitressin at this time. In the fowl, pitocin causes a fall in blood pressure. From a practical point of view a great advantage has been gained by the separation of these two principles in relatively pure form, for the effect upon the uterus can now be secured without a rise in blood pressure which it is often advisable to avoid.

Either pitressin or pitocin causes hyperglycemia, but which one will have the greater effect depends largely on the species. In rabbits pitressin has the greater hyperglycemic action, whereas in dogs pitocin is more effective. The rise in blood sugar induced by these principles is due to the breakdown of glycogen (glycogenolysis) in the liver.

Functions of the posterior lobe

Though a posterior lobe extract when injected produces very definite effects, such might not represent the physiological actions of the gland within the body. In other words, the effects following injection might be due to substances which, though obtainable by extraction, were merely incidental and not principles of a true internal secretion. Proof that any given effect was hormonal would be the demonstration that removal of the gland produced a contrary effect which could be corrected in turn by injection of

⁷ A Standard Pituitary Powder with which the oxytocic and pressor activities of a given pituitary preparation can be compared is obtainable from the United States Bureau of Chemistry. The official solution of Pituitary (Posterior Pituitary Injection, U.S.P. XII) of the Pharmacopeia of the United States contains 5 mg. of the standard powder per cubic centimeter. An international unit of oxytocic activity or of pressor activity is defined as the amount of activity, oxytocic or pressor, respectively, obtained by the

extraction of 0.5 mg. of the standard powder. The official Solution of Pituitary therefore contains 10 international units per cubic centimeter. This is also the strength of commercial preparations.

the extract. There is little definite evidence, for example, that in mammals the posterior pituitary secretes a pressor substance which maintains the normal blood pressure; and little to suggest that it is concerned with capillary tone, as was suggested by Krogh from experiments upon the frog. It is true that in the latter species and in the toad the posterior lobe does appear to be essential for the maintenance of capillary tone. Dilatation of the cutaneous vessels occurs in these animals after total hypophysectomy but not after removal of the anterior lobe alone.

The isolation of an oxytocic principle from the posterior lobe led, as it was bound to do, to the theory that the elaboration and discharge of such a principle by the pituitary constituted an important factor in the birth mechanism, serving to stimulate the uterine contractions and expel the fetus at the end of the period of gestation. This conception of posterior lobe function, attractive and plausible though it was, appeared to be refuted by certain observations. Allan and Wiles, for example, reported that normal parturition occurs in hypophysectomized cats, and Selye, Collip and Thomson found that though the period of gestation in rats was prolonged after hypophysectomy, no abnormality in the birth mechanism was detectable. Bell and Robson demonstrated an oxytocic principle in the blood of pregnant cows, women in labor and in non-pregnant rabbits, but since there was no relation between the concentration of this substance and any period of gestation, concluded that it was not concerned in the initiation of labor.

Such negative findings aroused scepticism as to a physiological relationship between the pituitary and the parturient uterus. However, this uncertainty has been largely dispelled by recent work. Haterius and Ferguson, experimenting with rabbits from 2 to 80 hours *post partum*, observed increased frequency and amplitude of the uterine contractions upon electrical stimulation of the pituitary stalk. The response closely resembled that induced by pitocin and was obtained after spinal transection, vagotomy and severance of both splanchnic nerves. It was abolished by destructive lesions placed in the infundibulum. These results indicate that the oxytocic principle of the pituitary is a true hormone. The continuous activity of the uterus in the puerperal rabbit appears in the light of the results of later experiments of Ferguson to be due to pituitary secretion initiated reflexly from the pelvic viscera, for the contractions undergo progressive diminution in amplitude after inter-

ruption of the afferent pathways, by section of the pituitary stalk or of the spinal cord above the 12 lumbar segment. Fisher and his colleagues have also found previously that after section of the hypothalamohypophyseal tract in cats the expulsive movements of the uterus at term were extremely sluggish. We know that this operation reduces almost to the vanishing point the action of the principles of the posterior pituitary.

Other significant facts lending support to this conception of posterior pituitary function just outlined are, the insensitivity of the uterine cervix to pitocin, and the influence of the female sex hormones upon the action of the oxytocic principle, namely, the depression of uterine sensitivity by the latter induced by progesterin and the great sensitivity conferred by estrin (p. 748). Very suggestive in this connection, also, is the discovery of Cohen and Marrian (p. 749) that estrin is present in the blood and excreted in the urine as an inactive compound (glycuronide of estrin) in pregnancy until just before the onset of labor when it appears in the free (active) form.

Expansion of the melanophores in amphibia and of the erythrophores in the minnow is also undoubtedly a hormonal effect, as is also the *antidiuretic action*.

THE SOURCE OF THE POSTERIOR LOBE SUBSTANCE AND THE PATHWAY OF ITS SECRETION

This is a question which has not been finally settled. The earlier work of Herring, of Cushing and Goetsch and others suggested that the cells of the pars intermedia and pars tuberalis elaborate the hormone or hormones, and that the hyaline bodies (p. 722) seen in these regions represent ripened cells filled with secretion. Geiling and Oldham, on the contrary, are convinced that the pressor, oxytocic and antidiuretic hormones are formed, not in the pars intermedia, but in the posterior lobe itself. Since the discovery of neurohormones (e.g., acetylcholine and sympathin) the absence of tissue of a glandular nature from this part of the pituitary is no obstacle to the acceptance of such a view and, as Geiling points out, the adrenal medulla is of neural origin. Another reason for believing that the neurohormonal tissue, probably the pituicytes, elaborates the posterior pituitary principles is afforded by the experiments of Fisher and his colleagues already referred to. After section of the nerve fibers in the infundibular stalk degenerative changes confined to the posterior lobe appear, and the pressor, oxytocic and antidiuretic principles are greatly

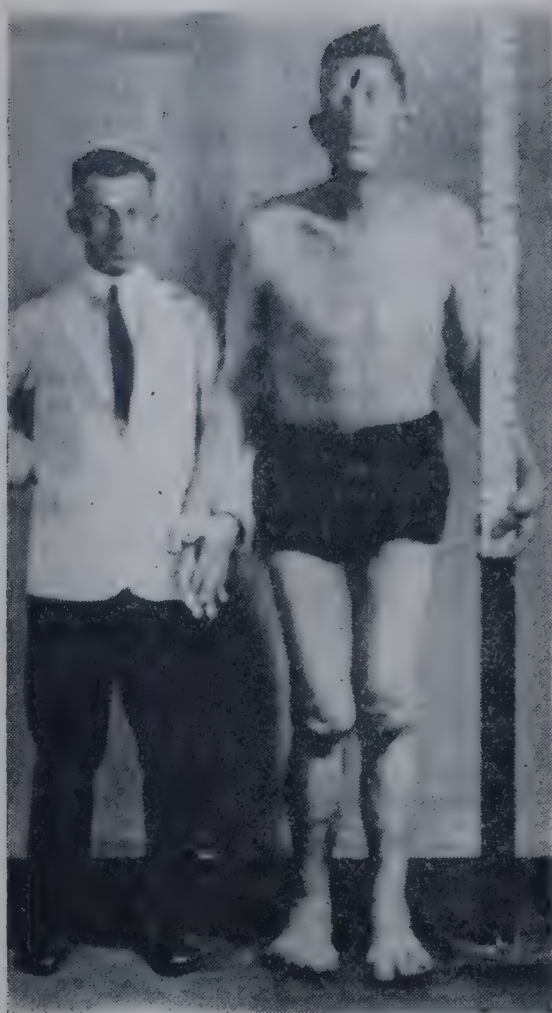
minated, whereas the pars intermedia contains the normal amount of melanophore-expanding principle. Many believe that the hyaline bodies described by Herring are artifacts, but whatever their nature and function may be, an experiment performed by Maddock indicates that they traverse the posterior lobe and infundibular stalk to be discharged into the third ventricle. When a compressing clip was placed upon the infundibular stalk numbers of hyaline bodies gathered, although blocked, on the pituitary side of the clip. Injections of India ink particles have been seen to traverse the pars nervosa and stream up the stalk, which strongly suggests that this is the pathway taken by the posterior lobe hormones. Hyaline bodies in the act of discharging into the ventricle have also been described. Detection of the posterior pituitary principle in the cerebro-spinal fluid by means of the oxytocic and melanophore tests have been reported by some workers, others, however, have failed to confirm the observation. The recent experiments of Zondek indicate that oxytocin leaves the pituitary via the infundibular stalk. This principle was recovered from the walls of the third ventricle in the region of the autonomic centers but from nowhere else outside the pituitary.

Circumstantial evidence for the view that the posterior lobe hormone is discharged into the ventricular system has been furnished by Cushing. He found that the injection of commercial pituitrin into the lateral ventricle of man produced the most striking effects, which commenced within five minutes of the injection. These effects resemble in several respects those characteristic of parasympathetic stimulation, and are quite different from those resulting from the intramuscular injection of pituitrin. They include: (a) flushing of the skin and most profuse sweating, (b) fall in rectal temperature from about 99.0° to 94.0°, (c) nausea, vomiting and contractions of the small intestine, (d) rise in blood pressure after an initial fall and some increase in heart rate, (e) salivation and lacrymation, (f) fall in metabolic rate (from 3 to 31 per cent) within 1½ hours. These effects are not due to histamine. Comparable effects have been produced by Fulton in the monkey. The intraventricular injection of pilocarpine (a drug which stimulates structures innervated by parasympathetic nerves) causes comparable effects. Atropine, which abolishes parasympathetic effects, prevents the customary results following the intraventricular injection of either pituitrin or pilocarpine. Furthermore these agents have not their usual action in persons in whom the tissue

of the hypothalamic region has been destroyed by disease, or in persons under the influence of an anesthetic such as avertin, which is believed to act upon the hypothalamus. Penfield has reported manifestations similar to those described above in a patient with a lesion (tumor) in the region of the hypothalamic nuclei; he refers to the condition as *diencephalic autonomic epilepsy*. On the basis of his results Cushing conceives that the secretion of the posterior lobe passes into the cerebro-spinal fluid of the ventricle and diffuses through the nervous tissue to act upon the parasympathetic center in the hypothalamus (tuber cinereum). On the other hand, the secretion of the posterior lobe is controlled by impulses arising in higher nervous centers and relayed to the gland through the hypothalamic nuclei (see p. 882). This conception of a nervous-hormonal synergism finds its analogy in the sympatho-adrenal system in which impulses flowing along sympathetic pathways cause the liberation of adrenal secretion, which in turn reinforces the action of the sympathetic.

DISORDERS OF THE PITUITARY IN MAN

Derangements of pituitary function may take the form of overactivity or of deficiency. In the former case tumors composed of functioning endocrine tissue are frequently the cause of the disorder; in the latter, atrophy or degeneration of the specific secreting cells, either primarily or as the result of mechanical pressure by tumors, may be responsible. A pituitary tumor of the anterior lobe may be composed of any of the cellular elements of the gland—*chromophobe*, *acidophil* or *basophil* adenomas. Squamous-celled growths (craniopharyngeomas) may also arise from epithelial rests—remnants of Rathke's pouch—near the root of the infundibular stalk. As a result of the confined position of the pituitary within the sella turcica the entire gland is likely to suffer from pressure effects when one of its parts becomes enlarged. For this reason and on account of the proximity of other important structures, e.g., hypothalamus and optic chiasma, and the proclivity of tumors to invade or press upon neighboring structures, the manifestations of a pituitary tumor are not always referable simply to the part of the pituitary originally involved. Any function—growth, sex, water elimination, or the metabolism of carbohydrate or fat, presided over by the pituitary-hypothalamic mechanism may therefore be disturbed by a lesion in this region. Nevertheless, the site wherein the tumor arises



The following is a short classification of pituitary disorders—

Anterior lobe	{	overactivity	{ Acromegaly Giantism Pituitary basophilism— Cushing's disease
		deficiency	{ Dwarfism Pituitary cachexia— Simmond's disease Acromicria
Posterior lobe deficiency or hypothalamic lesion			Diabetes insipidus
Anterior lobe deficiency together with posterior lobe deficiency or hypothalamic lesion			Dystrophia - adiposo-genitalis (Fröhlich) (a) Infantile or juvenile type (b) Adolescent or adult type

ACROMEGALY

This condition was first described by Pierre Marie in 1885. It is due to the excessive elaboration of the growth hormone (p. 724) during adult life, i.e., after the usual age of full skeletal growth (fig. 290). An adenomatous tumor of the anterior lobe composed of acidophil cells is responsible for the hypersecretion. The characteristic features of the condition are: (a) overgrowth of the bone

FIG. 290. Acromegaly, together with enlarged stature—acromegalic giantism. (After Cushing and Davidoff.)

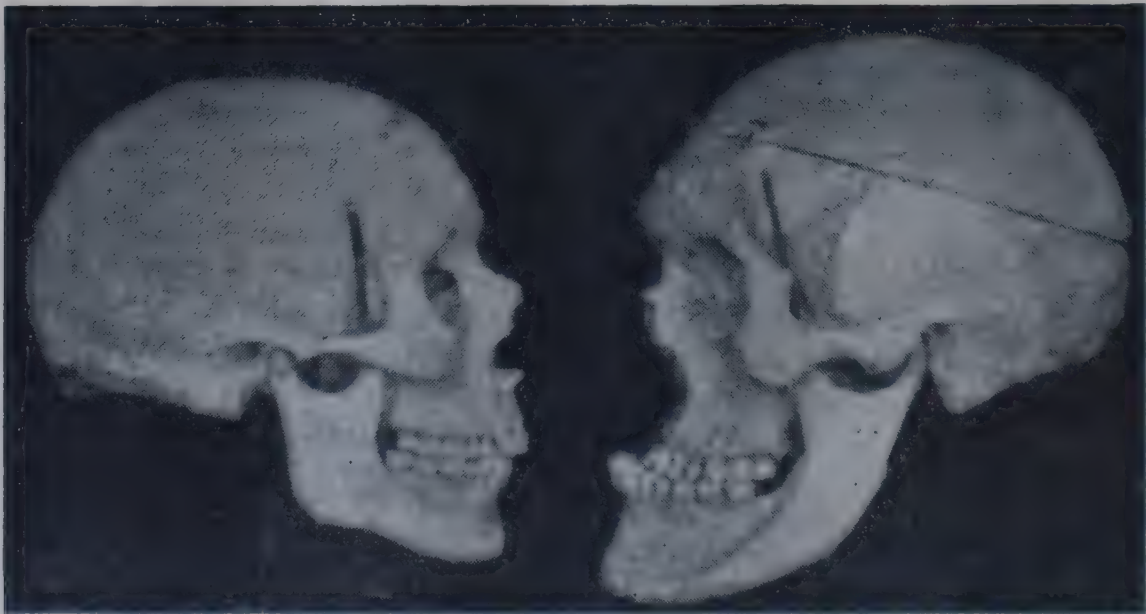


FIG. 291. Skulls of a normal person (left) and of an acromegalic (right). (After Cushing and Davidoff.)

and the nature of the cells of which it is composed do very often determine the predominant features of the condition, and certain fairly well defined groups of symptoms (syndromes) are recognized. To these may or may not be added symptoms referable to pressure upon, or to irritation or destruction of, near-by nervous structures.

of the hands, feet and face. Of the latter, the mandible, nasal bones and supraorbital ridges are especially involved (fig. 291). The feet and hands are greatly increased in size, the latter being usually broadened and the fingers thickened. Under the X-rays, the terminal phalanges appear tufted, thus resembling a wheat-sheaf in shape.

bowing of the spine (kyphosis) is common. The soft tissues of the nose, lips, forehead and scalp are thickened, the latter being thrown into folds or wrinkles (bulldog scalp). There is a general overgrowth of body hair. (b) Atrophy of the gonads and suppression of the sexual function (amenorrhea in women, impotence in men). In the earlier stages there may be evidence of increased sexual function. (c) Enlargement of the viscera (splanchnomegaly). The tongue, lungs, thymus, heart, liver and spleen are greatly enlarged. The thyroid, parathyroids and adrenals may show hypertrophy or adenomatous growths. Hyperthyroidism may be present in the early stages. (d) Glycosuria and hyperglycemia are common, and a condition indistinguishable from diabetes of pancreatic origin may be present. The metabolic rate may be raised by from 10 to 70 per cent; the specific dynamic action of protein is not altered (p. 554).

GIANTISM

Giantism is due to a pituitary lesion of a similar nature to that responsible for acromegaly, but the condition arises in pre-adult life, i.e., before ossification is complete (fig. 292). A general overgrowth of the skeleton results and the production of persons of enormous stature—7 or 8 feet or more in height. The limbs are usually disproportionately long. The viscera are not enlarged out of proportion to the frame unless, as is sometimes the case, the giantism is accompanied by the characteristic features of acromegaly, as may occur after adolescence.

PITUITARY BASOPHILISM (CUSHING'S DISEASE)

This very rare condition is generally attributed to an anterior lobe adenoma composed of basophil cells⁸ (fig. 293). Its main characters are: (a) Obesity of the trunk (especially of the abdomen), face and buttocks, but not of the limbs. The fatty deposits are frequently tense, tender and painful. Purplish striae, due to distention, are present over the lower abdomen. (b) Cyanosis of the face, hands and feet, pigmentation of the skin and excessive growth of hair. Women may grow a mustache or a beard. (c) Loss of mineral from

⁸ Susman found, however, that in the postmortem examination of a large number of pituitaries, small basophil adenomas were present in 3.1 per cent, though no signs of basophilism was observed during life. Crook also states that a basophil adenoma or a general increase in basophil cells is an inconstant finding in Cushing's syndrome, but that hyaline degeneration of these cells (with or without adenoma) is invariable.

the bones, with softening or brittleness. The softening often involves the dorsal vertebrae and leads to kyphosis. (d) Vascular hypertension. (e) Suppression of sexual functions. (f) Hyperglycemia and glycosuria and in some cases increased urinary excretion of nitrogen. (g) Atrophy of testes or ovaries and sometimes hypertrophy of the adrenals (cortex or medulla or both). In view of the commanding position which the pituitary occupies in the endocrine system it is highly probable that some of the features of the condition are due to the secondary disturbances in the functions of other endocrines. The skeletal

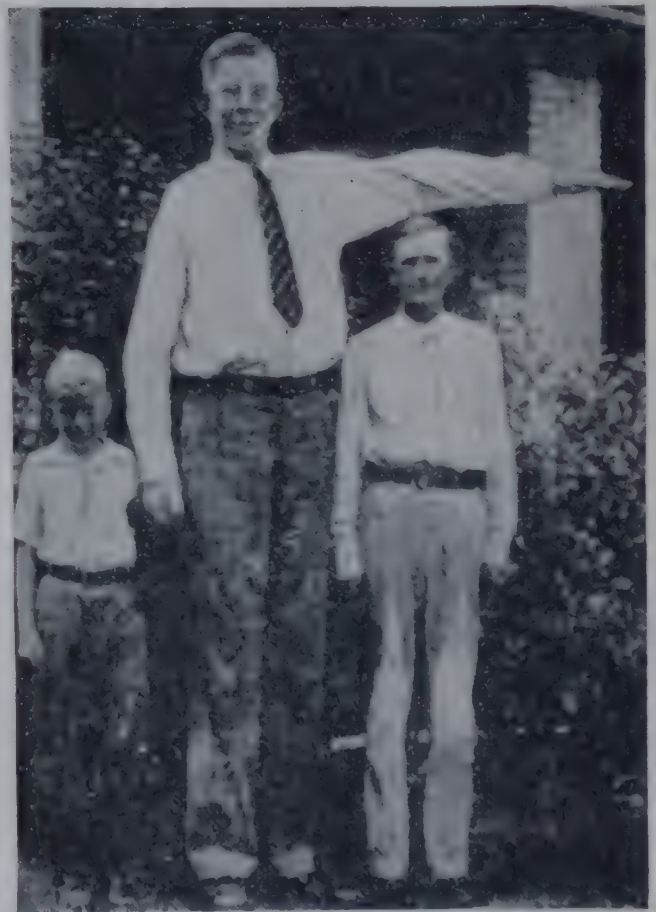


FIG. 292. Giantism. (After Best and Taylor, *The Human Body and its Functions*.)

decalcification, for example, suggests parathyroid overactivity, nevertheless such a relationship is not indicated by histological examination of the parathyroids in subjects of basophilism, degenerative rather than hyperplastic changes in these glands having been observed. The depression of the sexual functions and genital atrophy are difficult to explain, since they are the reverse of what might be expected from the supposed functions of the basophil cells (p. 756). It is possible, however, that the changes seen in the parathyroids and gonads represent an exhaustion atrophy resulting from overstimulation. The vascular hypertension and the adrenal hypertrophy already

mentioned strongly suggest that the adrenals are overstimulated by the pituitary excess. Moreover, primary disease of the adrenal cortex (e.g., tumor) may produce a clinical picture almost indistinguishable from that of pituitary basophilism (fig. 274, p. 698). In other words, some of the outstanding clinical features of the condition termed pituitary basophilism are due directly, apparently, to adrenal activity and may therefore arise either from primary adrenal disease, or secondarily as a result of a basophil tumor of the pituitary.



FIG. 293. Pituitary basophilism. On left, at 20 years of age; right, 5 years later at height of the disease. (From Cushing, after Turney.)

DWARFING

The arrested skeletal development which results from deficiency of the growth hormone of the anterior pituitary is spoken of as the *Lorain* type of infantilism (fig. 294). These dwarfs are usually, though not invariably, undeveloped sexually. They do not show deformity or as a rule mental inferiority, and are generally not unattractive in appearance. Sometimes, however, they are wizened and except for their miniature stature appear older than their years (*progeria*). The anterior lobe dwarf at adult age may be no more than 3 or 4 feet in height. During infancy and childhood, the ossification centers as observed by radioscopy appear normal and dentition is not delayed. The relative proportions of the different parts of the skeleton are not far from normal though they tend toward those characteristic of childhood, the head being large relatively to the

body. Some encouraging results have been reported from the treatment of this type dwarfism during early childhood with anterior pituitary preparations.

According to Evans the dwarfing seen in cretinism is also due essentially to pituitary deficiency—a result of the absence of the normal stimulative effect of the thyroid hormone upon hypophyseal function. (See footnote, p. 725.)

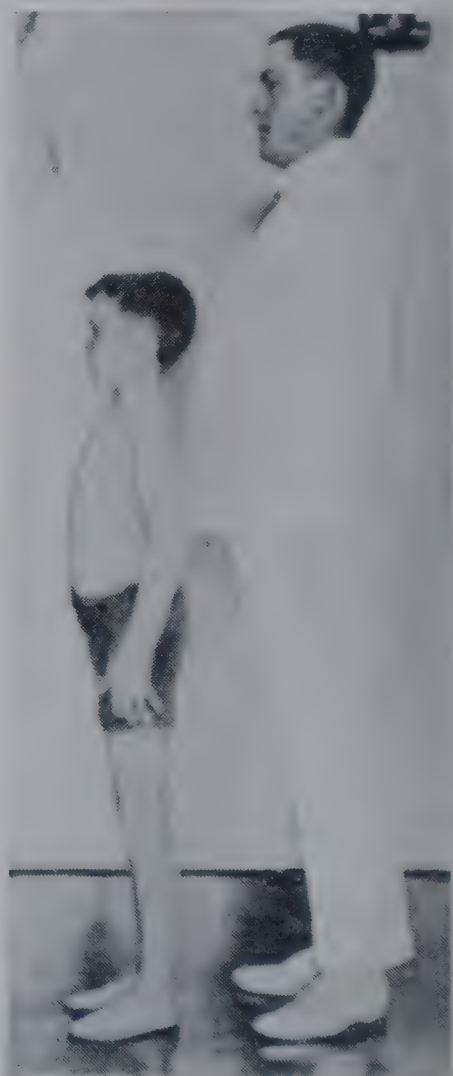


FIG. 294. Infantilism due to anterior lobe deficiency. Age 21 years. Man on right, 5 feet 7 inches. (After Lisser.)

PITUITARY CACHEXIA (SIMMONDS' DISEASE)

This rare disease was first described by Sir Simonds of Hamburg. It is due to atrophy and degeneration of the anterior lobe. The main features of this disease form a picture which may be best described as that of a premature and rapidly developing senile decay (fig. 295). This may be briefly summarized as follows:—
General appearance—loss of axillary and pubic hair; hair of the head prematurely gray and sparse; loss of teeth; skin of face wrinkled and dry; of great emaciation; smallness of hands and feet and shrunken appearance of the facial features. (a) *Anemia*. (c) *Low metabolic rate and hypoglycemia*.

Amenorrhea or impotence. (e) *Mental deterioration, muscular weakness, death in coma.* (f) *Atrophy of the gonads and a general smallness of the internal organs (splachnomicria).*

Acromicria. This is the antithesis of acromegaly. The bones of the face and extremities are small, delicate and fragile. Other features are, loss of hair, depression of sexual functions and cyanosis of the extremities. It is due probably to disease of the acidophilous elements of the anterior lobe with consequent deficiency of the growth hormone. It occurs in adults, and is, after the period of skeletal growth, and thus bears the same relationship to dwarfism as acromegaly bears to giantism.



FIG. 295. Pituitary cachexia. Photograph on left, patient aged 42 years; photograph on right, the same man at the age of 34 years. (From Zondek. *Disorders of the Endocrine Glands*, Arnold, London.)

DIABETES INSIPIDUS

Diabetes insipidus is a condition in which large quantities of urine of very low specific gravity, 1.002 to 1.006, and low chloride content, are excreted. In an ordinary case the daily output of urine is 4 or 5 liters, but daily amounts several times these figures have been reported. A corresponding increase in the fluid intake occurs and thirst is often intense. The condition frequently accompanies tumors of the pituitary or hypothalamic region. It has been ascribed to posterior lobe deficiency, since it is relieved by injections of pituitrin and in earlier experiments upon animals was a common result of hypophysectomy. It has been shown, however, by Bailey and Bremer, and later by others, that in animals puncture of the hypothalamus in the region of the tuber cinereum without any apparent injury to the pituitary causes polyuria. Diabetes insipidus also ensues in conditions (epidemic encephalitis) involving the hypothalamic region. On the other hand, the

aforementioned antidiuretic effect of pituitrin and the experiments of Maddock, in which the condition was induced in animals by the application of a clip to the pituitary stalk, point to deficiency of the posterior lobe of the pituitary as a factor. It is more correct, however, to look upon diabetes insipidus as the result of a disorder affecting the integrity of the hypophyseal-hypothalamic mechanism rather than as being dependent specifically upon either the pituitary or the hypothalamus. Involvement of one or other element, or of the nervous connections between the two would therefore cause the disease. Fisher, Ingram and Ranson found, for example, that a lesion interrupting the supra-optico-hypophyseal tract of nerve fibers resulted in diabetes insipidus together with atrophy of the cells of the supra-optic nucleus and of the posterior lobe of the pituitary. The atrophic posterior lobe was found to be almost devoid of antidiuretic, oxytocic and pressor principles.

The failure of total hypophysectomy to produce diabetes insipidus is due, according to the widely accepted theory of von Hann, to the secretion by the anterior lobe of a hormone which antagonizes the post-pituitary antidiuretic factor, i.e., to the production of a *diuretic* principle. Von Hann based his view on the postmortem records of twenty subjects with lesions involving the posterior lobe. In nine, no functioning anterior lobe tissue remained and these had not suffered from diabetes insipidus. The experimental results of Richter accord with these findings. Total hypophysectomy in rats was in no instance followed by permanent diabetes insipidus, whereas this condition was invariably produced by removal of the posterior lobe alone. This theory implies that the excretion of water by the kidney is normally governed through a nice balance established between the activities of the anterior and posterior lobes—a balance which is upset by (a) removal of the latter, (b) by interruption of its nerve connections with the hypothalamus, or (c) by the injection of an anterior lobe extract after total hypophysectomy. It has been found that an intact thyroid gland is necessary for the experimental production of diabetes insipidus; the condition once established is abolished by thyroidectomy, but can be induced again by thyroid administration. An experiment performed by Keller suggests that the diuretic action of the anterior lobe is brought about through its thyrotropic hormone. When anterior lobe extract was administered daily to a hypophysectomized animal the water intake did not show

the anterior lobe of the pituitary, which accounts for the sexual immaturity and dwarfing, and of the hypothalamus (or posterior pituitary). The experiments of Smith with hypophysectomized rats and of other investigators point to injury of the hypothalamus rather than of the posterior lobe being chiefly responsible for the obesity. Marked obesity is also a feature of certain hypothalamic disorders in man unassociated apparently with any disease of the pituitary itself. *Dysphagia adiposo-genitalis* appears in two forms according to the age at which it develops—the *infantile* or *prepuberal* and the *adolescent* or *adult*.



FIG. 297. Male aged 8. Hypopituitarism following whooping cough, with characteristic growth and sex defects and obesity; Fröhlich's syndrome. (After Gardiner-Hill.)

THE INFANTILE OR PREPUBERAL TYPE (fig. 297). This type may occur in children of any age before puberty. It may be the result of an inherent defect of the pituitary, of atrophy of the secretory cells by pressure (e.g., by tumors), injury (e.g., a penetrating wound) or of some infectious disease. Polyuria and a high sugar tolerance are frequent accompaniments of the disease. The subjects are lethargic or somnolent and often of subnormal intelligence. They usually have voracious appetites and especially a craving for sweets. The "fat boy" of *Pickwick Papers* was undoubtedly an example of this condition. The younger the age of the child at which the disease commences the greater, obviously, will be the degree of stunting. When the dwarfing is of high grade this

combined with the obesity makes a very striking picture. These subjects are human counterparts of Smith's rats in which the pituitary was destroyed (and the hypothalamus presumably injured) by chromic acid injections.



FIG. 298. Extreme case of obesity, due to pituitary or hypothalamic disease. (After Timme.)



FIG. 299. Laurence-Biedl-Moon syndrome. Note the presence of six toes. (After Weiss.)

The name of Brissaud is sometimes associated with the disease as seen in children around the age of puberty.

THE ADOLESCENT OR ADULT TYPE. Male subjects of this condition are often effeminate in disposition and appearance. The excess fat has a feminine distribution, the adiposity being notice-

able chiefly in the mammary region, buttocks, thighs and over the mons veneris. The hair over the pubis and in the axillae is sparse or absent; the skin of the face and the body is smooth, soft and hairless; the hips are broad. In female subjects the obesity is often extreme, a weight of 300 pounds being not very unusual (fig. 298). In both sexes the feet and hands are small and "pretty," the finger tips being slender and tapering with narrow pointed terminal phalanges. The extremities thus give a picture the reverse of that seen in acromegaly. The basal metabolic rate is often subnormal and sugar tolerance increased.

Diabetes insipidus is a common, and narcolepsy (p. 884) an occasional, accompaniment.

LAURENCE-BIEDLE-MOON SYNDROME

This condition, hitherto attributed to pituitary deficiency, is now believed to be due to involvement of the hypothalamus. Since it bears resemblance to the condition described in the last paragraph it is convenient to consider it here. The chief features of the disease are: obesity, sexual infantilism, retinitis pigmentosa, polydactylism, mental deficiency and a family tendency (fig. 299).

CHAPTER LXII

THE ENDOCRINE ORGANS OF SEX. THE THYMUS AND PINEAL GLANDS

THE CHARACTERS OF SEX

The sex glands—testes or ovaries—are known as the *gonads*. They are the *primary organs of*

They furnish the male or female sex cells (spermatozoa or ova) upon which the *ultimate* maleness or femaleness of the animal depends.

The sex, and so the type of sex gland, which is developed is ordained, however, at the earliest possible time in the history of the individual, namely, when the parental ovum and spermatozoon conjugate. The determining factor is the type of chromosome (X or Y) in the sperm cell. The cells of the human body possess 48 chromosomes—24 pairs. In the case of the male one of these pairs contains a small chromosome, designated Y. The other chromosome of this pair is large like those in the other pairs and is referred to as X. In the female, the chromosomes in all pairs are the same, that is, X chromosomes. When the male and female germ cells mature each receives only half the number of chromosomes. Some sperm cells will therefore contain a Y, others an X chromosome. An ovum, of course, can contain only an X chromosome. Fertilization of an ovum by a sperm cell possessing a Y chromosome, results in a zygote containing a chromosome of each type. The body cells of the individual to which this cell ultimately gives rise will therefore contain each a pair of XY chromosomes; the offspring will be male. If the ovum is fertilized by a sperm cell containing an X chromosome the offspring will be female (XX). Certain diseases and defects are linked with the X chromosome of the male. Among such sex-linked diseases are hemophilia and color blindness. They appear in the male but are transmitted by the female who does not herself show the disease. For example, a man afflicted with hemophilia if he marries a normal woman does not transmit the disease to his sons (XY), for the X chromosome received from the mother does not carry the defect, nor does the Y chromosome derived from the father. The daughters, however, have received an abnormal character in the X chromosome derived from the father as well as a normal one from the mother. But, since the abnormal character is recessive, it is "suppressed" by the dominant normal character,

and the daughters are free from the disease, though their cells must contain the chromosome carrying the defect. When therefore the daughters marry and an ovum is fertilized by a sperm cell containing an X chromosome the daughters of the next generation again show no abnormality; but should a Y sperm fertilize the ovum and an XY (male) zygote result, the child will show the disease if one of the abnormal X chromosomes of the mother has paired with the Y from the father. The Y chromosome does not offset the effect of the abnormal X chromosome. It should be remembered that since the mother possesses two X chromosomes, a normal and an abnormal one, it is an even chance which one the child will receive.

Those organs, other than the sex glands, which are essential for procreation, such as the external genitalia, as well as the uterus, Fallopian tubes and vagina of the female and the seminal vesicles and prostate of the male, are spoken of as the *accessory organs of sex*. Other characters of sex only make their appearance at the time of sexual maturity (puberty), e.g., the growth of hair upon the pubis of the human male or female, the development of the mammary glands in women, the development of the antlers of stags, the distinctive plumage of birds and the psychic manifestations of sex in man and in animals. These are spoken of as the *secondary sex characters*.

EFFECTS OF EXCISION OF THE SEX GLANDS OR GONADS—CASTRATION—SPAYING

Removal of the gonads (castration) from a young animal prevents the mature development of the accessory sex organs and the secondary sex characters fail to make their appearance. The effects of castration upon the secondary characters are evident even in such simple animal forms as the earthworm and the hermit crab. Castration of male frogs prevents the appearance of the sexual changes which normally occur during the mating season. The thumb-pad and the fore-limb muscles do not hypertrophy, the clasping reflex cannot be elicited and the animal does not emit its characteristic croaking sound. Transplantation of the excised testicular tissue into another part of the animal's body prevents the occurrence of these

castration effects. The sexual development of birds and mammals is profoundly affected by castration. The castrated Leghorn cockerel (capon), for example, has a greater proportion of body fat than the normal bird, while the comb, wattles and barbles, and the sex instincts do not develop. Development of the spurs and plumage, however, is not prevented. Corresponding effects of gonadectomy are seen in the young turkey-cock and in the young of other avian species. Removal of the ovaries from the young hen (spaying)¹ causes the development of spurs, a comb resembling that of the cock, and male plumage. The spayed duck assumes the plumage of the drake.²

The effects of castration upon young cattle, horses and stags are well known. Castration of young bulls causes an increase in size of the skeleton and a greater deposition of fat. The mature development of the accessory organs is prevented. The antlers of young stags do not develop after castration and female deer after atrophy or disease of the ovaries may develop horns. Castration of boys before puberty retards ossification of the epiphyses of the long bones with consequent enlargement of the stature. The lower limbs become disproportionately long. There is also adiposity, the fat tending to become feminine in distribution. The larynx is not prominent as in the mature male and the voice remains high-pitched. The hair fails to grow upon the face and body, but is unusually plentiful on the head. The penis remains infantile and sexual feeling is suppressed. Ovariectomy is followed by corresponding effects; if performed before puberty the characteristic feminine attributes do not appear, the girl tends to become mannish in type, the accessory organs fail to develop fully and menstruation does not occur. In animals subjected to this operation before puberty the estrous cycles do not ensue. If the operation is performed after puberty the estrous cycles are suppressed and the accessory organs atrophy. In women after the age of puberty ovariectomy is followed by changes characteristic of the menopause (p. 762), namely, amenorrhea, atrophy of the sex organs and obesity.

Sex desire in higher animals and in the human subject is not, apparently, dependent entirely

upon the gonads, for it is sometimes retained in eunuchs and in women who have been ovariectomized after marriage though removal of the ovaries before puberty, i.e., before the accessory organs of sex have reached maturity, or in virgin women after puberty, suppresses the libido. Stone found that a certain proportion of a series of male rats castrated after sexual maturity had been attained, pursued the female and were capable of copulating during a subsequent period of eight months. Rowe also cites the instance of a man in whom the sex libido was not abolished twenty-five years after the testes had been excised. Prepuberal removal of the testes prevents the development of sexual desire.

The freemartin

The effect of the secretion of the gonads upon the sexual development of the embryo is shown in the case of twin calves when these are of opposite sexes. In such cases the male twin is always normal but the female, in the majority of cases, shows abnormalities of the accessory organs. The uterus is small and underdeveloped, the clitoris is enlarged and penis-like; the gonads are rudimentary and may resemble testicles and in some instances structures resembling vasa deferentia and seminal vesicles are present. The abnormal female showing such intersexual characters is called a *freemartin*. Keller and Tandler in Austria and Lillie in America have made a study of a number of such cases. They found that as a result of the fusion of the chorions, a direct communication between the circulations of the male and female embryos exists. According to Lillie, the fusion of the chorions is seen at an early stage of development, when the embryo is no more than 10 or 20 mm. long. In the rare case in which the female twin was normal a communication between the two circulations did not exist and no masculinization of the female twin is therefore attributed to the action of the internal secretion liberated by the gonads of the male. In order to explain the fact that masculinization of the female occurs but never feminization of the male, it is supposed that the hormone of the testis is elaborated at an earlier stage of development than is that of the ovary. Masculinization of guinea-pigs has been induced by the injection of testicular hormone into the fetuses *in utero* (Dantchakoff). Ivy and his colleagues produced corresponding effects in rat fetuses by means of male hormone treatment of the mother during gestation; feminization of male fetuses was also effected by antenatal treatment with female hormone (oestradiol-dipropionate, p. 749).

Transplantation or grafting experiments

If the excised sex gland (testis or ovary) is transplanted to another situation in the body and the otherwise inevitable effects of castration are prevented. This fact, first demonstrated by Lillie

¹ The terms ovariectomy and castration are also applied to this operation.

² Male plumage is considered to be the basic or neutral type. Its development is suppressed by the female sex hormone, the female type of plumage then appearing. Hence it is that male plumage appears after ovariectomy and persists after removal of the testes.

449, proves conclusively that the sex gland (male or female) furnishes an internal secretion. Transplantation of the gland from its normal position into a new situation in the same animal is called *autotransplantation*. The grafted tissue usually lives. This operation has been performed in the human female after the apparent complete excision of the ovaries. Fertility resulted. The grafting of the gonad into a new animal of the same species is called *homotransplantation*. This operation is not so successful, though a certain proportion of homotransplants survive and perform their functions, for a time at any rate. This way feminization of the capon or masculinization of the bilaterally ovariectomized hen can be effected by the transplantation of the gonad of the opposite sex. Transplantation of the gonad into the body of a member of another species is known as *heterotransplantation*. It is the least successful type of transplantation. In some cases, however, histological evidence of the survival of the transplant for some months has been obtained, but atrophy occurs eventually.

Development of the gonads

The ovaries and testes arise from the celomic epithelium covering the inner aspect of the Wolffian duct. The epithelial cells of this region assume a columnar form; they proliferate to form several layers which constitute the *germinal epithelium*. The mesoderm underlying the germinal epithelium becomes thickened to form the *genital ridge*. Fingers of mesoderm grow upwards into the overlying germinal epithelium while columns of the latter cells grow into the mesoblastic tissue. There is thus an interlocking of epithelium and mesoblastic cell masses. The epithelial columns, or *genital cords*, as they are called, later become broken up into *cell nests*. From these, the *Graafian follicles* of the ovary or the *seminiferous tubules* of the testes are developed. A layer of the germinal epithelium also comes to cover the surface of the ovary. The mesoblastic tissue surrounding the islands of the primitive gonad gives rise to the stroma and vascular tissue of the ovary or testis.

Structure of the ovary. The adult ovary is about the size and shape of a shelled almond and consists of a stroma of connective tissue which carries the blood vessels and in which are embedded a number of follicles called the *Graafian follicles*—in different stages of development. The stroma also contains a few smooth muscle fibers. The surface of the ovary is covered with a layer of epithelial cells—the *germinal epithelium*—continuous with the epithelium of the general peritoneum. Irregular groups of epithelial-like cells are also scattered throughout the ovarian stroma of many animals. Groups of these so-called *interstitial cells*, absent from the human ovary, though scattered throughout, are similar in appearance, and probably also in function, are present.

The Graafian follicles. Just as in the embryo, the germinal epithelium sends columns of cells into the underlying mesoderm, so in later life the germinal

epithelium covering the ovary sends small groups of its cells into the ovarian stroma. One cell of the group develops into a primitive ovum around which the remainder become arranged in a circular row. This body—the *primordial follicle*—which so far has no cavity and is about 0.5 mm. in diameter, migrates deeper into the stroma. Two more layers of cells derived from the surrounding stroma are now formed which encircle the ovum and the layer of cells immediately in contact with it. The outer of these layers—the *theca externa*—is fibrous; the inner—the *theca interna*—is vascular and more cellular. The original layer of cells in immediate contact with the ovum at the same time multiply to form a mass of cells several layers deep in which two concentric zones can soon be

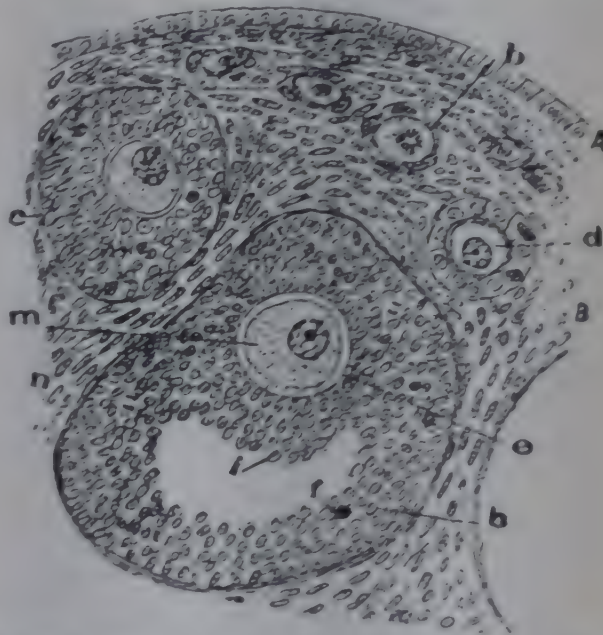


FIG. 300. Section of ovary of rabbit. A, germinal epithelium; a, young primordial Graafian follicle; b, ovum in mitosis; d, another primordial follicle but more advanced; c, ovum with membrana granulosa; m, ovum almost mature with discus proligerus (i) and membrana granulosa (b). (After Cajal, Textbook of Histology.)

distinguished. Later, these become partly separated from one another by the collection of fluid (liquor folliculi) between them to form an inner and an outer zone. The inner-zone in immediate contact with the ovum is called the *discus proligerus* (fig. 300). The outer zone forms a lining for the maturing follicle and is known as the *membrana granulosa*. As it becomes larger and the changes just described, which are spoken of as *follicular maturation* or *ripening*, progress, the follicle migrates again outwards, and when quite matured projects from the surface of the ovary. Rupture of the follicular wall follows and the ovum, which in the meantime has undergone partial maturation (extrusion of first polar body) is discharged and conveyed along the Fallopian tube to the uterus. The subsequent history of the Graafian follicle is given on page 750. Large numbers of small follicles containing immature ova are present in the ovary from birth. Ripening of the follicle and discharge of the ova do not occur, however, until puberty. In the mature ovary there appear at regularly recurring periods crops of

premordial follicles. But only a small proportion of these advance to complete maturation and discharge their ova. In the human species, no more than one or two ova are as a rule discharged each month. The remaining follicles reach various stages in the ripening process and then undergo degenerative changes (*atretic follicles*). Each of the latter is finally replaced by fibrous tissue derived from the theca interna, a small scar (*corpus fibrosum*) alone remaining. The factors which determine the rupture of the ripe follicle are not definitely known. The accumulation of fluid and the consequent increase in intra-follicular pressure is probably a factor in some animals, or the contraction of the smooth muscle fibers of the stroma may play a part. In most species, including man, the follicle ruptures spontaneously, but in the rabbit, cat and ferret ovulation occurs only after copulation.

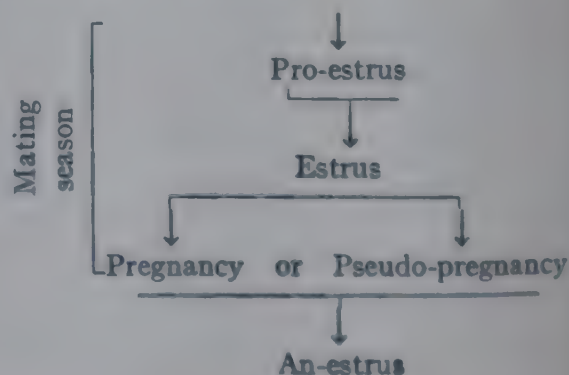
THE SEXUAL LIFE OF FEMALES

Three sexual periods of different lengths occur in the female mammal: (1) A single long period occupying the greater part of the animal's life. It commences at *puberty*, at which time the first ovulation occurs, the accessory organs of reproduction mature, sex desire is aroused and the secondary sex characters appear. It ends with atrophic changes in the ovary and accessory organs. In women the termination of this period is called the *menopause* (p. 762).

(2) A period which recurs once or oftener each year, known as the *mating* or *breeding season*. In most species it is only during this time, or during a part of it, that the female will receive the male. The duration of the mating season and the number of times it occurs annually vary in different species. In the dog, for instance, two such periods of about six weeks' duration occur each year (spring and autumn), while in certain other species they occur more frequently, and in others again only once, and may be of long or of short duration. In the human, reproduction is not confined to any one part of the year, though a study of birth statistics shows that fertility is greatest at certain periods (April to June). It has been suggested that in primitive man a mating season corresponding to this time of year did exist.

(3) *The estrous cycles*. These are periods of sexual activity which in animals occur once or oftener in each breeding season. The first cycle commences at puberty. In women, higher monkeys and anthropoid apes they are represented by the menstrual periods. Animals such as the bitch, in which a single estrous cycle extends throughout the breeding season, are called *monestrous*. *Poly-estrous* animals, on the other hand, are those such

as the domestic cat, the mare, cow, sow, rat and mouse, in which two or more cycles, separated by short periods of sexual quiescence, occur in succession during the breeding season. In a monestrous animal the following phases of the estrous cycle are distinguished. (a) *Pro-estrus*, or period of "coming on heat." There are usually swelling and congestion of the external genitalia together with growth and increased vascularity of the uterus. There is, as a rule, some enlargement of the mammary glands and, in the dog and cow, bleeding from the vagina. During this stage of the cycle the Graafian follicles are undergoing maturation preparatory to rupture. (b) *Estrus*,³ or "period of desire." The female receives the male and ovulation occurs. The term "heat" is commonly applied to the combined periods, pro-estrus and estrus. (c) *Pseudo-pregnancy* or *pregnancy*. The changes in the uterus initiated during the previous periods progress and in some animals, e.g., the bitch, rabbit and ferret, there occur pronounced proliferation and secretory activity of the uterine glands, hypertrophy of the mucosa and a great increase of the uterine blood supply. The growth of the mammary glands is stimulated. This phase of the sexual cycle is known as pseudo-pregnancy. The uterine changes, which are similar to those occurring in the premenstrual period of the human subject are looked upon as anticipating the arrival of a fertilized ovum. If this fails to ensue the newly-formed uterine fabric breaks down, the debris is discharged and the uterus returns to its resting state. If impregnation of the ovum occurs the uterine changes persist and merge into those characteristic of the pregnant state. (d) *Anestrus* is the period of sexual quiescence. It follows pregnancy or pseudo-pregnancy and coincides with the period elapsing between either of these periods and the next mating season. The monestrous cycle may be illustrated as follows.



³ *Estrus*, L = *gad-fly*, with figurative meaning of frenzy or intense desire.

polyestrous animals the short intervals of quiescence separating the estrus cycles are called *anestrous periods*. The term *anestrus*, as in the case of monestrous species, refers to the longer periods of rest between the mating seasons. Copulation and pseudo-pregnancy do not occur spontaneously in certain animals, e.g., cat, rabbit and ferret, but only after copulation. Though the onset of estrus in some species is quite obvious, in rodents it is difficult to detect by the ordinary means. Stockard and Papanicolaou, however, discovered that the vaginal mucosa of the guinea pig underwent certain changes (cornification of epithelium and disappearance of leucocytes) coinciding with the onset of estrus. Similar changes occur in the vagina of the rat and mouse. By the examination of a smear of the vaginal secretions the stages of the estrous cycle can be readily followed in these animals. Leucocytes which are present in smears taken during the anestrous or anestrus period are absent from the vaginal secretions during pro-estrus and estrus, but large squamous (cornified) cells appear.

OVARIAN HORMONES

These are: (1) *estrin*, also known as the *follicular hormone* or *female sex hormone*, and (2) the *corpus luteum hormone* or *progestin*. The follicular hormone is concerned particularly with the first part of the estrous cycle, the corpus luteum hormone with the latter part (pseudo-pregnancy), and with the pregnant state.

ESTRIN—THE FOLLICULAR HORMONE

The evidence derived from ovariectomy and transplantation experiments had made it clear that the ovary furnished an internal secretion which was responsible for the sexual development of the female, yet the results of experiments with ovarian extracts had been inconclusive until the work of Allen and Doisy in 1923. They obtained a potent ether extract from the liquor folliculi aspirated from hog's ovaries which was capable of inducing estrus in immature animals. The success of these workers was to a large extent due to the employment of a precise method for the demonstration of estrus, namely, the vaginal smear technique described above. Other investigators, for the most part, had relied upon uterine effects as a means of testing the activity of their extracts. The name *oestrin* was suggested by Parkes and Bellerby for this ovarian hormone. It is usually called estrin on this side of the Atlantic.

The physiological action of the follicular hormone may be listed as follows: (1) It induces estrus in immature animals and in ovariectomized adult animals, or in normal adult animals during anestrus; there result in consequence, hypertrophy of the uterus and proliferation of its glands (fig. 301), vaginal changes, growth of the mammary glands (p. 765), rhythmical contraction of the muscle of the uterus and Fallopian tubes, psychic and other phenomena associated with the estrous period; it sensitizes the uterine muscle to the action of pitocin. (2) It prevents the otherwise inevitable atrophy of the accessory reproductive



FIG. 301. Effect of injection of follicular extract into eight-week-old rabbits. Animals were litter sisters. No. 807 received 2 mg. of extract No. 805 not injected and killed at the same time as No. 807 for control. No. 806 received 1 mg. of extract daily for four days and No. 809 1 mg. daily for eight days. No. 808, uninjected control, killed on same day as No. 809. (After Doisy, Ralls, Allen and Johnston.)

organs in ovariectomized animals. (3) It is believed to be responsible for the development of the secondary sex characters which in some species are such prominent features of the mature female. (4) Its injection into the adult *male* rat induces retrogressive and degenerative changes in the genitalia, and retards the development of sexual maturity in immature male rats; it causes atrophy of the cock's comb. These "antimasculine" effects are probably exerted through the inhibition of the gonadotropic activity of the anterior lobe of the pituitary (p. 753). The growth effect of the pituitary is also abolished, but thyrotropic activity is unaffected. Zondek found that prolonged treatment with estrin causes great enlargement of the

pituitary which contains large amounts of gonadotropic and growth principles; estrin, therefore, apparently effects the utilization or liberation, rather than the production of these factors. (5) Estrin is believed to be largely responsible for the enormous growth of the uterus during pregnancy. When pregnancy is confined to one horn of the rabbit's uterus, that horn alone increases in size. It is thought therefore that estrin, which is in high concentration in the placenta, may act locally upon the uterine tissue rather than through the general circulation. On the other hand, it may well be that the mechanical effect of distension is necessary for sensitization of the uterus to the action of the hormone, for the introduction of paraffin pellets of a certain size into the uterine cavity induces a localized hypertrophy. Estrin does not stimulate the ovaries; continued injections actually reduce the size of the latter and of the testes, an effect attributed to suppression of the gonadotropic principle of the pituitary. (6) Estrin exerts no notable effects upon the circulation, respiration, body growth or basal metabolic rate. (7) If, after menstruation has been abolished in monkeys by ovariectomy, a series of injections of estrin is given and then stopped abruptly, menstruation occurs a few days later. During the estrin treatment of these ovariectomized animals, phenomena appear, analogous to those appearing during the estrous period of lower animals, e.g., endometrial changes, redening and swelling of the external genitalia, and the vaginal smear shows cornified cells and the absence of leucocytes. (8) A synergic action between estrin and the oxytocic principle of the posterior pituitary has been demonstrated; after the administration of estrin to a mouse toward the end of pregnancy a dose of pitocin which ordinarily is ineffective causes a powerful contraction of the uterus. (9) Estrin acts as a "primer" for the action of the corpus luteum hormone (progestin, p. 750) and is apparently necessary also for the maintenance of the corpus luteum during pregnancy. When administered in large doses, however, it antagonizes the latter's action in bringing about the progestational changes in the uterine mucosa. (10) Prolonged dosage with the follicular hormone raises the blood calcium, especially in the fowl. (11) Estrin induces water retention, an increase in blood volume and of the water content of the muscles. Ovariectomy results in a loss of water and a diminished volume of blood which is restored to normal by estrin administration.

The origin and distribution of estrin (oestrin)

The elements of the ovary responsible for the production of estrin are not definitely known. Its presence in high concentration in liquor folliculi and the fact that follicular maturation coincides with the onset of estrus, point to the follicular cells (probably of the theca interna) as being the chief source. Yet these cells cannot be solely responsible, for Parkes showed that estrus continues at regular intervals after the follicles have been completely destroyed by X-rays; moreover, estrin can be extracted from the ovarian stroma alone. The interstitial cells in the latter situation may be one source of the hormone. One of the most remarkable features of estrin is its very wide distribution in animal tissues, though there is no evidence that in the non-pregnant state estrin is produced anywhere but in the ovary. It is found in the blood, muscles and urine of both pregnant and non-pregnant females, in the urine of adult males and in the testes, the testes and urine of stallions being among the richest known sources (Zondek). It is present in very high concentration in the urine of pregnant women after the first 2 or 3 months. In the late months around 300,000 or more international units are excreted daily. It is also obtainable in large amounts from the urines of pregnant mares and monkeys. The human placenta also contains large quantities of estrin which are believed to be actually manufactured by this organ, for women ovariectomized during the later months of pregnancy continue to excrete large amounts of the hormone in the urine. Estrin is present in the corpus luteum, in the fetal membrane and in amniotic fluid; it has been demonstrated in human chorionic vesicle containing an embryo 12.5 mm. in length.

Chemistry and terminology

Doisy and his colleagues and Butenand independently, isolated estrin in crystalline form from urine. Upon analysis it was found to have the empirical formula $C_{18}H_{22}O_2$ and to possess a ketone and a hydroxyl group. A second form of estrin containing one more molecule of water and having the formula $C_{18}H_{24}O_3$ was isolated from urine shortly afterwards by Marrian. The latter contains 3 hydroxyl groups but no ketone. It is less active than the previous form. Doisy gave the name *theelin* to the first of these forms; others speak of it as *ketohydroxyestrin* or *estrone*⁴ (oestrone).

⁴The advisory committee on nomenclature of endocrine principles appointed by the Council of Pharmacy and Chemistry of the American Medical Association.

the second form, called *theelol* by Doisy, is also referred to as *trihydroxyestrin* or *estriol* (oestriol); it is transformable to estrone by dehydration *in vacuo* with potassium bisulphate.

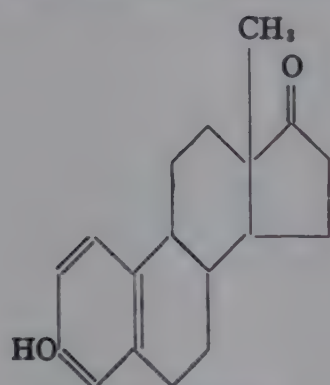
Estradiol (dihydroxyestrin, dihydrotheelin) ($C_{18}H_{24}O_2$) is a third crystalline compound which is first prepared in the laboratory by reduction of the ketone group in estrone to a hydroxyl group. There are three isomeric forms α , *iso* and β . The α -form possesses much the greater activity of the three. Since its artificial preparation α -estradiol has been isolated by MacCorquodale and his colleagues from sows' ovaries and by Doisy and his associates from the urine of pregnant women, it is now generally believed to be the true estrogenic hormone. Winterstein and his associates have isolated the beta-form from the urine

group in the 3 position in estradiol with benzoic acid gives a product possessing a more prolonged physiological action than the original compound.⁶ This substance—the *benzoate of estradiol*—is known commercially by various names. *Estradiol-dipropionate*, another laboratory product, has an even greater and more prolonged action.

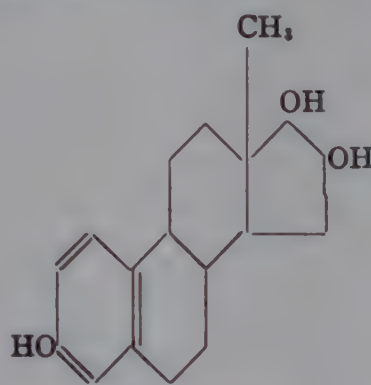
Emmenin, isolated by Collip and his associates from human placenta is an ester (probably the glucuronide) of estriol. It is active by oral administration.

The term estrin is customarily employed as a general physiological designation for follicular hormone preparations regardless of their precise chemical constitution.

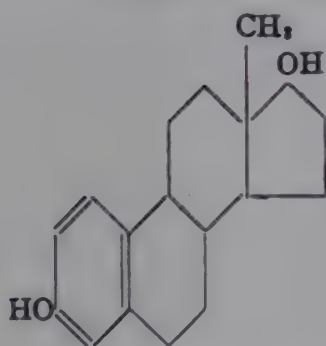
The structural formulae of four of the estrogenic compounds just described are as follows:



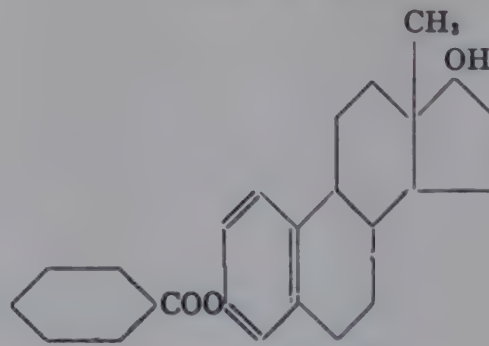
Ketohydroxyestrin,
(Theelin or estrone)



Trihydroxyestrin,
(Theelol or estriol)



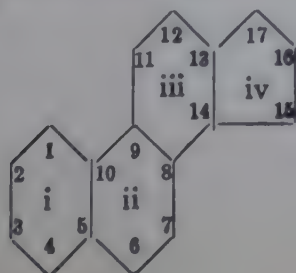
Dihydroxyestrin or
estradiol



Benzoate of estradiol

of pregnant mares. Iso-estradiol is a synthetic compound and has not been obtained from a natural source. The replacement of the hydroxyl

association recommend the following chemical names, 3-hydroxy, 17-keto $\Delta^{1,3,5}$ -estratriene; 3, 16, 17-trihydroxy $\Delta^{1,3,5}$ -estratriene and 3, 17-dihydroxy $\Delta^{1,3,5}$ -estratriene, respectively, for estrone, estriol and estradiol. The numbering is shown in the following skeleton formula.

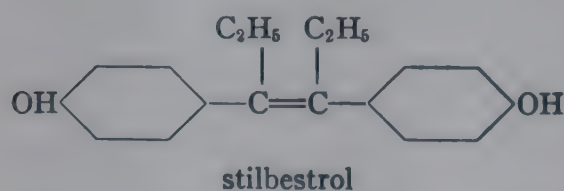


The presence in the blood during pregnancy of large amounts of estrin has always been something of a physiological puzzle, but some enlightenment has come through the discovery of Cohen and Marrian that estriol is excreted in the urine of pregnancy conjugated with glycuronic acid. This compound—the *glycuronide of estriol*—is physiologically inert, but is hydrolyzed, active estriol being freed, by the usual methods (involving acidification and heat) employed in isolating the hormone from urine. It was found, moreover, that the quantity of combined estriol in the urine of

This is probably due to the fact that the benzoate as compared with the other compounds is less readily attacked and inactivated by the liver.

women just before the onset of labor became reduced, whereas that in the active (free) state became greatly increased. The significance of these findings in respect to the activation of the birth mechanism is obvious (p. 734). The conjugation of estriol with glycuronic acid at once suggests a detoxicating process in the liver whereby the uterus is protected from the action of an excess of circulating estrogenic hormone.

Estrin and the hormones of the corpus luteum and testes belong to the class of sterols, being related chemically to the bile acids, to cholesterol and to calciferol. Starting with ergosterol, estrone was synthesized by Marker and his associates in 1936. Estrogenic substances have been obtained from a wide variety of sources other than animal tissues and fluids. Among some of these sources are petroleum, peat and lignite, yeast, rape seeds and pussy willows. Substances—benzanthracene compounds—with estrogenic properties and structural formulae suggestive of those given above have also been synthesized. The synthetic estrogenic compound, 4:4'-dihydroxy- α β diethylstilbene, known generally as *stilbestrol*, was introduced by Dodds and his associates in 1938 and has since come into clinical use. This substance exhibits an estrogenic potency between two and three times greater than that of estrone; its activity is reduced by only 50 per cent when given orally. Its formula is given below.



The relation between cancer production and estrogenic substances

Some of the estrogenic benzanthracene compounds are capable of causing cancer when painted on the skin, and coal tar which it will be recalled induces skin cancer is also estrogenic. These recent developments, associating carcinogenic and estrogenic effects and demonstrating the close chemical relationship between cancer-producing agents and the physiological substances mentioned, are highly suggestive. The production within the body (as a result of an abnormality in sterol metabolism of some material of the benzanthracene type which may play a rôle in the genesis of cancer, is a possibility which comes to mind. "The cell proliferation which characterizes the estrous state is in some respects reminiscent of the

early stages of malignant growth" (Cook and Dodds); so also is the development of the decidua tissue of early pregnancy which, as we shall see is dependent upon the hormone of the corpus luteum. The following suggestive observations may also be cited in this connection.

(a) Cori found that ovariectomy of mice belonging to a strain showing a very high susceptibility to mammary cancer caused a marked reduction in the incidence of the disease.

(b) Lacassagne produced mammary cancer in male mice, which ordinarily are not susceptible to the disease by the injection of large doses of an estrogenic hormone. This observer also states that differences exist between the estrous cycles of mice showing a high susceptibility to cancer and of those showing a low incidence of the disease: Loeb and his associates were unable, however to detect any characteristic feature of the cycles in the various strains of mice which could be definitely related to the occurrence of cancer.

(c) In women, cystic ovaries and apparently hyperovarian function, have been found in frequent association with an hypertrophied endometrium.

(d) In monkeys prolonged treatment with theelin has resulted in atypical growths of the epithelium of the uterine cervix.

Method of assay and standardization of estrogenic activity

It has been the practice to assay the activity of estrogenic preparations upon ovariectomized rats or mice, a unit being defined as the minimal quantity of the material required to induce estrus, as determined by the vaginal smear technique, in the test animal. A rat or a mouse unit has not, however, an absolute and definite value but shows wide discrepancies between different laboratories, owing to variability in the detail of the assay technique employed by individual workers. The Commission on Biological Standardization of the League of Nations has therefore defined a unit of estrogenic activity as the activity of 0.1 microgram (0.1 γ) of estrone. Three such *international units* are approximately equivalent to the original rat unit of activity as defined by Allen and Doisy. The dosage of estrone required to produce a physiological effect is related to the body weight. In order therefore to induce a response in a woman possessing no endogenous supply of the hormone something like 500,000 international units would be required.

THE HORMONE OF THE CORPUS LUTEUM

After the discharge of the ovum the cavity of the ruptured Graafian follicle becomes occupied by a clot of blood. The small body formed in this way is sometimes spoken of as the *corpus hemorrhagicum*. The clot is soon replaced by a mass

containing a yellow lipoid material (luteal cells). These are derived from the proliferation of the cells of the membrana granulosa (p. 745) of the theca interna.⁶ The follicle with its content of luteal cells constitutes the *corpus luteum* (fig. 302). The circumference of the follicle at this time has become more vascular and capillaries penetrate into the yellow cell-mass. The transformed follicle may now be looked upon as a temporary internal secreting organ. If fertilization of the ovum does not occur the life of the



FIG. 302. Section of corpus luteum showing luteal cells under high magnification (from Parkes, *The Internal Secretions of the Ovary*, by permission of Livingmans, Green & Co.).

corpus luteum is short. In the human it persists for about 10 days and then retrogresses. Its capillaries become obliterated, the luteal cells disintegrate and are replaced by fibrous tissue; nothing then remains of the follicle but a pale scar—the *corpus albicans*. On the other hand, if fertilization of the ovum results the corpus luteum continues to grow and in women attains a diameter of three-quarters of an inch or more by the middle of pregnancy. It then commences to shrink and is finally absorbed by about the seventh month.

Functions

The corpus luteum is essential to gestation. In some species (e.g., the rabbit and rat) it persists throughout pregnancy and abortion occurs if it is destroyed. In others (e.g., the human subject,

monkey, cat and guinea-pig) it is not indispensable after the earlier months of gestation (4 or 5 months in women). It is responsible for: (1) Changes in the uterine mucosa preparatory to the implantation of the ovum—pseudo-pregnancy of lower mammals and the premenstrual changes of primates. After implantation of the ovum the hormone of the corpus luteum is necessary for the development of the maternal placenta (decidua). (2) Growth of the mammary glands. (3) The suppression of estrus and ovulation.

The evidence for the foregoing is as follows: (a) Born observed that corpora lutea were not present in the ovaries of mammals which did not form a true placenta (monotremes). (b) Frankel, following up this hint, showed that if the corpora lutea were destroyed in pregnant rabbits abortion resulted.⁷ (c) If pregnant rabbits are injected toward the end of term with urine of pregnancy (p. 755), a fresh crop of corpora lutea appears and the gestation period is prolonged by several days; the fetuses become 50 per cent larger than normal and more mature (Snyder). A similar effect can be produced with the purified hormone of the corpus luteum. (d) Loeb discovered that stimulation of the uterine mucosa of the non-pregnant guinea-pig by means of a glass bead or a thread during the development of the corpora lutea resulted in the growth of a small mass of decidual tissue (deciduoma) at the point of stimulation. This effect, now known as the *Loeb reaction*, could not be obtained after the corpora lutea had been excised or during a phase in the estrous cycle when they were absent. Even transplanted uterine tissue responded to stimulation in a similar way if the ovary contained corpora lutea. Other observers have obtained corresponding results in the rat, rabbit and dog. Teel was able to produce deciduomata in the unmated rat by injections of a luteinizing extract (p. 753) of the anterior pituitary. The inference to be drawn from these experiments is, that the contact of the fertilized ovum with the endometrium is the natural stimulus which in the presence of a corpus luteum causes the formation of decidual tissue. (e) In the rabbit which does not ovulate except after copulation a corpus luteum does not form unless this act takes place, nor does pseudo-pregnancy occur. If, however, a corpus luteum is produced by the artificial rupture of a ripe follicle, or, as first shown

⁶ In most species, but probably not in all, the theca interna shares in the production of luteal cells.

⁷ In certain species, including the human, in which the corpus luteum degenerates in the later months of gestation ovariectomy at this time does not cause abortion.

by Ancel and Bouin, ovulation is induced by mating with a sterile (vasectomized) male, the characteristic endometrial changes of pseudo-pregnancy appear. (f) The mammary gland, or transplanted mammary tissue, shows increased growth during pregnancy and pseudo-pregnancy which has been correlated with the growth of the corpus luteum. Mammary growth ceases at the end of pseudo-pregnancy when the corpus luteum retrogresses and is slight or absent if the latter has been prevented from forming. In rabbits, artificial rupture of ripe follicles causes corpora lutea to form in some instances but not in others; only in the former does mammary growth occur. (g) The results of several experiments indicate that the corpus luteum inhibits follicular maturation and suppresses ovulation. It is well known that squeezing the corpora lutea from the cow's ovary by manipulation through the rectum hastens the onset of the next estrous period. Destruction of the corpus luteum in the guinea-pig acts similarly. Also, a greater quantity of the follicle-stimulating hormone (p. 754) of the anterior pituitary is required to induce ovulation in the presence of corpora lutea than in their absence. The function of the corpus luteum in suppressing ovulation provides against a second pregnancy being superimposed upon the first (superfetation).

The foregoing evidence for the function of the corpus luteum has been supplemented by the researches of Corner and Allen. These observers obtained an extract from the ovary of the pig which contained the active principle of the corpus luteum; this they called *progestin*. Injections of the principle into animals produces the following effects: (a) A perfect imitation of the progestational changes (pseudo-pregnancy) in the uterine mucosa of castrated adult rabbits.⁸ The uterus of the immature rabbit or of an adult animal which has been castrated some time previously, however, is unresponsive unless first "primed" by a previous course of estrin injections. In order to produce the typical progestational development of the uterine mucosa in the castrated monkey it is also necessary to administer both hormones; menstruation then occurs (Smith and Engle). Kaufmann showed similarly that in castrated women a premenstrual endometrium can be produced only by the administration of both the follicular and the corpus luteum hormones. The follicular hormone (estrin)

apparently initiates the progestational change causing vascularization of the mucosa and proliferation of the glandular elements, while the corpus luteum stimulates secretory activity and brings about the final alterations in the mucosa necessary for the implantation and nourishment of the fertilized ovum. Estrin also appears to be necessary for maintaining the growth of the corpus luteum of pregnancy and for the continued action of progestin upon the uterine mucosa. (b) Rabbits castrated early in pregnancy abort; injections of progestin enables them to be brought to full term. (c) Softening and relaxation of the pelvic ligaments and separation of the symphysis pubis of the guinea-pig; these effects imitate those occurring in pregnancy and are not obtained in the absence of the follicular hormone. (d) Inhibition of the uterine response to pituitrin (Knaus reaction). When the uterus of a rabbit which has been treated with progestin is excised it does not contract when pituitrin (even in large quantities) is added to the bath in which it is suspended; definite relaxation may result. The muscle will still, however, respond to adrenaline or quinine. The motility of the uterus of the intact animal is also suppressed by progestin. The change in reaction of the uterus of certain species to adrenaline (p. 687), from inhibition to excitation when pregnancy occurs is evidently due to the corpus luteum hormone, for a similar reversal of uterine behavior to adrenaline can be effected by progestin injections. (e) Estrin and progestin are antagonistic; according to Allen 675 rat units of estrin are neutralized by 3 units of progestin. The motility of the uterus of an infantile animal or of a castrated mature animal is inhibited by progestin; the uterus of a mature animal with intact ovaries is affected to a much less extent by the corpus luteum hormone.

The clinical uses of progestin are considered on p. 764.

Chemistry of progestin (progesterone)

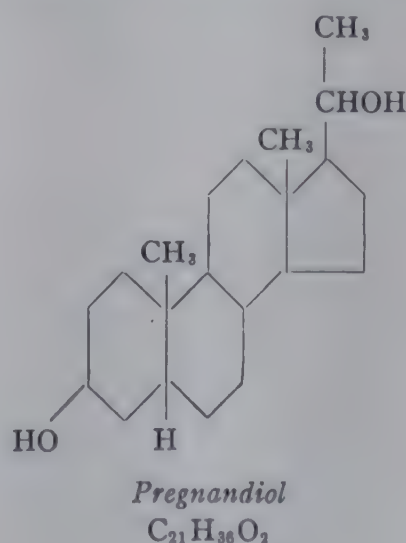
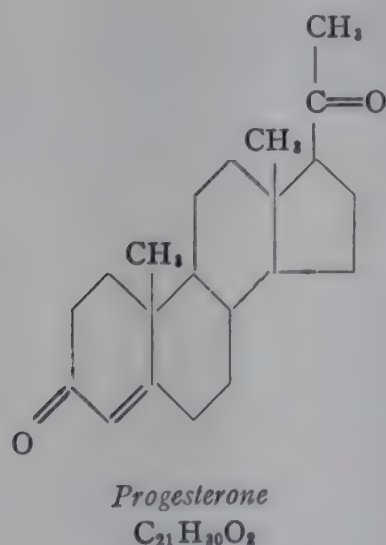
The active principle of the corpus luteum has been obtained in crystalline form. Its structural formula is shown below (compare with the formula for estrone and estriol on page 749, with that for testosterone given on page 771, and with the crystalline compounds of the adrenal cortex (p. 693)). This crystalline product has been named *progesterone*, the older name *progestin* being reserved for the unpurified luteal principle contained in ordinary corpus luteum extracts. Progesterone occurs in two isomeric forms alpha- and beta-

⁸ A unit of progestin is defined as the minimum quantity that is required, when divided into 5 daily doses, to produce in a 4 kg. castrated rabbit uterine changes equivalent to those of the 3th day of pregnancy.

progesterone. They are about equal in physiological activity.

Starting with a sterol (stigmasterol) obtained from a soy bean Butenandt and his associates have recently succeeded in completing the later steps in the synthesis of progesterone. It has also been prepared by Butenandt from the conversion of pregnandiol.

Pregnandiol is a physiologically inert reduction product of progesterone isolated from the urine of a pregnant woman by Marrian in 1929. Its very close chemical relationship to progesterone is evident from the formula shown above; it is readily convertible to progesterone in the laboratory. Only minute quantities of progesterone itself are found in blood or urine. Similarly to estriol and other derivatives of testosterone (p. 771) pregnandiol is excreted in conjugation with glycuronic acid (Mell and Marrian). Injected progesterone appears in the urine as pregnandiol glycuronide. The occurrence in urine in different phases of the human sexual cycle has been investigated by Towne and his associates who found it present as *pregnandiol glycuronide* in the luteal phase of the menstrual cycle, but not in the follicular and intermenstrual phases. The excretion of pregnandiol commences a day or two after ovulation, reaching a maximum about a week before the onset of menstruation and ceasing 2 or 3 days before. During pregnancy much larger quantities appear in the urine, the greatest excretion being during the eighth and ninth months. In certain cases of spontaneous abortion the excretion is less than normal, a fact pointing to defective production of the corpus luteum hormone.



The international standard of potency used in the assay of progesterone preparations is defined as the progestational activity of 1 mgm. of the international standard preparation of progesterone.

The test animal is an adult female rabbit which has been mated and then castrated, or an immature female rabbit which has been primed for 5 days previously with estrin.

THE GONADOTROPIC (GONAD-STIMULATING) HORMONES OF THE ANTERIOR LOBE OF THE PITUITARY, GONADOTROPINS

Several observations in the past have pointed to the anterior pituitary as exerting an influence upon sexual development. The gradual atrophy and suppression of the sex functions in diseases of the anterior lobe in man (acromegaly, Fröhlich's syndrome) and the atrophy of the gonads after hypophysectomy in animals are among some of these observations (fig. 303).

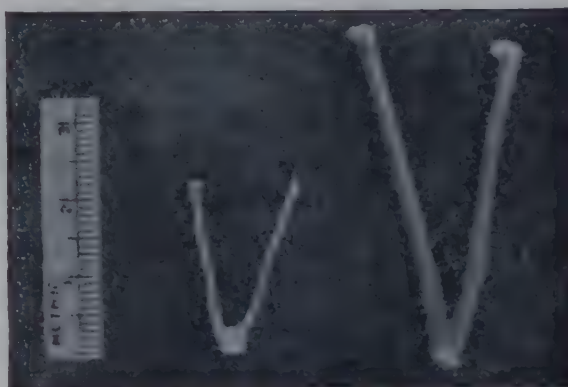


FIG. 303. Effect of hypophysectomy upon the uterus. On right, uterus of normal rat; on left, that of an hypophysectomized rat. (After Van Dyke, *The Physiology and Pharmacology of the Pituitary Body*. Chicago Univ. Press.)

In the earlier experiments of Evans and associates with the saline growth-promoting extract of the anterior lobe of the pituitary (p. 724) it was

observed that the Graafian follicles became enlarged and filled with luteal cells (fig. 304). Usually, of course, corpora lutea form only after ovulation, but in these animals the estrous cycles

were suppressed, the ova remaining imprisoned within the luteinized follicles (atretic corpora lutea). The extract was later shown to depress the sex instincts of males and to reduce the weight of the testes. The male animals, however, remained fertile. Ovulation in hens was inhibited. These effects upon the sex processes were shown later to be independent of the growth hormone, for it was possible to separate the extract into two fractions, one having an effect upon growth, the other having the luteinizing effect just described.

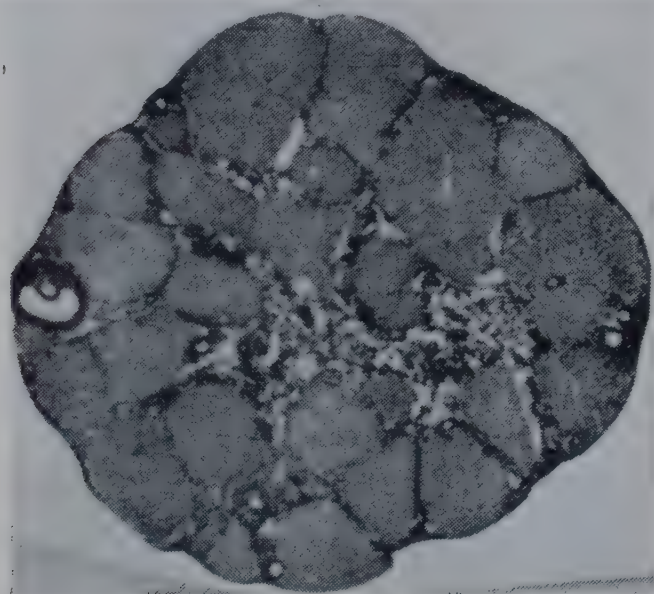


FIG. 304. Ovary of adult mouse injected with alkaline extract of anterior lobe of pituitary. Large numbers of corpora lutea are present, and few follicles (from Parkes, *The Internal Secretions of the Ovary*, by permission of Longmans, Green & Co.).

It soon appeared that another sex hormone possessing a quite different effect was present in the anterior lobe. Smith and Engle found that when *fresh* mammalian anterior lobe tissue was transplanted daily into immature female rats or mice, estrus was precipitated and ovulation stimulated. The ovaries enlarged to 10 times the normal size (fig. 305), and developed a large number of follicles which ripened and discharged a "shower" of ova (superovulation). Corpora lutea formed within the rupture follicles, reached a small size and then retrogressed. The vagina, which is not a complete canal in the immature rat or mouse, opened, its epithelium changed from the columnar to the squamous type and the uterus enlarged from 5 to 10 times. Ovulation and estrus were also induced in adult sexually quiescent females. The testes, seminal vesicles and penis of immature males were stimulated to increased growth, and gonadal atrophy which follows hypophysectomy in either males or females was prevented by the anterior lobe transplants. Zondek and Aschheim

about the same time performed similar experiments in Germany upon immature female mice and obtained comparable results, the effects being evident within 100 hours. They pointed out that

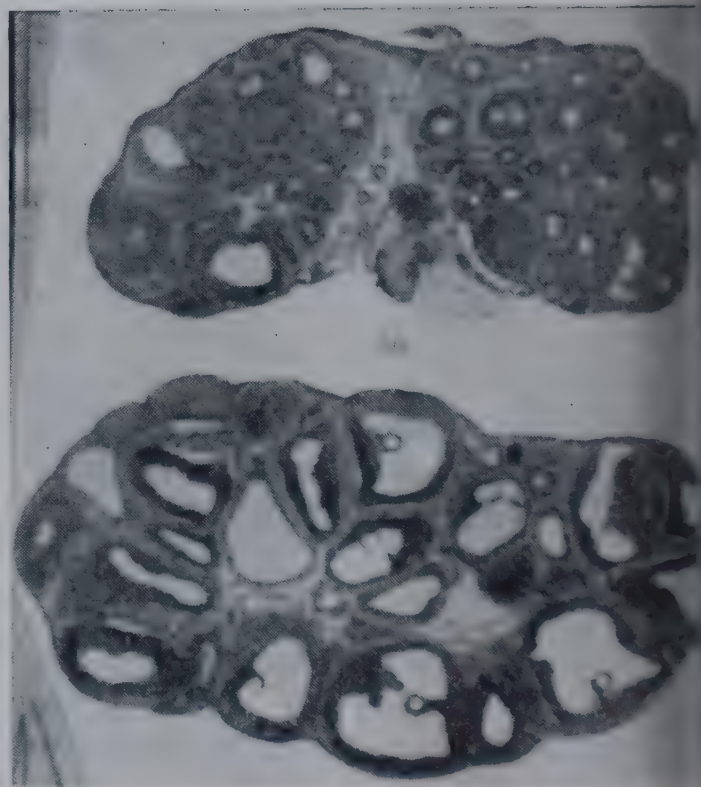


FIG. 305. Showing effect of anterior pituitary upon ovaries. On left, below, ovaries of rat after twelve implantations of fresh rat pituitary gland; above, ovaries of litter mate control rat. (After Collip). On right, below, follicular maturation induced in immature rat on twenty-ninth day by eight daily implantations of fresh pituitary gland; above, ovary of litter mate control. (After Smith and Engle.)

the ovaries must be intact in order for estrus to occur. The essential action upon the female by this anterior lobe hormone is therefore to *stimulate follicular maturation and cause the liberation of estrin*. Estrus and its associated phenomena are secondary to the action of the latter hormone.

Aschheim and Zondek also showed that both effects of effect, luteinization on the one hand, and follicular maturation (ripening) on the other, could be produced in female mice by injections of the blood or urine of pregnant women (see pregnancy at below). Later work has shown that the follicle-stimulating principle may be obtained by

of the ovarian follicle, namely, the epithelium of the seminiferous tubules; large numbers of sex cells in various stages of development, including mature spermatozoa, are produced. The luteinizing principle, on the other hand, acts apparently upon the interstitial cells of the testes which are analogous to the thecal cells of the ovary (p. 745).

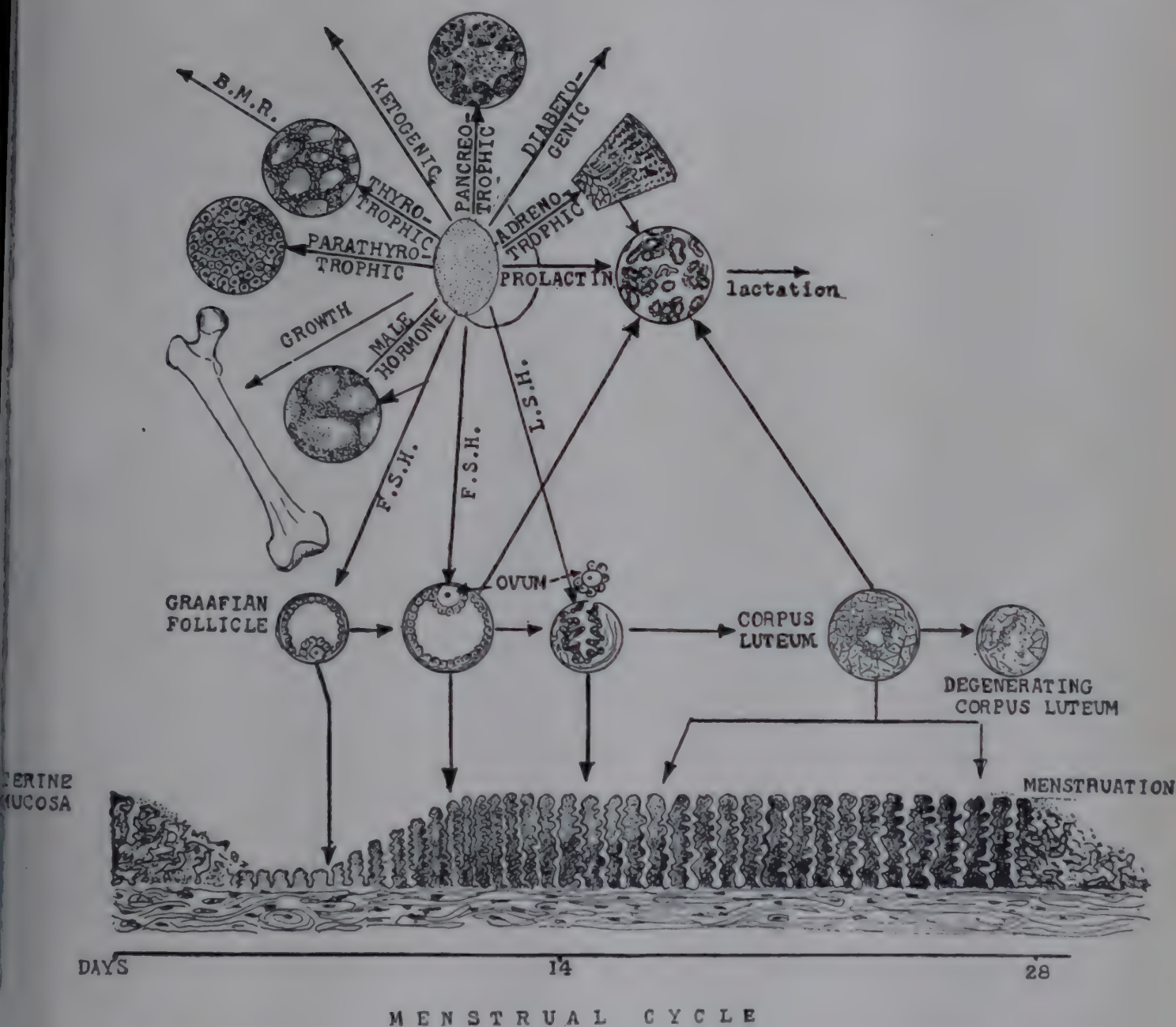


FIG. 306. Diagram summarizing the endocrine relationships of the anterior lobe of the pituitary

acid extraction of the anterior lobe. The follicle-stimulating hormone (whether in anterior pituitary or in pregnancy urine) was called *prolan A* and the luteinizing hormone *prolan B*. The gonadotropic principles are no longer referred to by these terms, but are known either as the *follicle-stimulating* and the *luteinizing hormones*, respectively, or as *gonadotropins I* and *II*.

The follicle-stimulating hormone also stimulates the tissue of the testes analogous to the granulosa

causing the liberation of the testicular hormone.* (See diagram, fig. 306.)

*Some workers believe that the gonadotropic functions of the pituitary are due to a single hormone and that the type of response obtained is dependent upon the dosage or upon the stage of the sexual cycle during which the treatment is given. The recent work of Wallen-Lawrence and of Fevold and Hisaw, and of a number of other workers have secured evidence strongly favoring the belief in two distinct hormones. They have obtained two nearly chemically pure preparations, the one having a follicle-stimulating action alone, the other causing luteinization.

The respective actions of the gonadotropic hormones of the anterior pituitary are tabulated below.

Follicle-stimulating hormone. ¹⁰	Ripening of follicles, superovulation, small corpora lutea.
	Production of estrin, phenomena of estrus.
	Proliferation of epithelium of the seminiferous tubules of the testes.
Luteinizing hormone:	Extensive luteinization, retained ova.
	Production of hormone of corpus luteum.
	Inhibition of estrin production, suppression of estrus. Stimulation of interstitial tissue of testes (p. 722).

These two hormones act synergically, the luteinizing principle being without effect unless preceded by the action of the follicle-stimulating hormone. The luteinizing principle is therefore inactive after hypophysectomy unless the animal has been primed with an estrogen.

It was shown by Bellerby that ovulation, which does not occur spontaneously in the rabbit, may be induced in this animal by injecting an acid extract of the anterior lobe. On the other hand, hypophysectomy of the rabbit one hour after copulation prevents ovulation, which normally occurs 10 to 12 hours after the act. Hypophysectomy performed later than one hour after copulation does not inhibit ovulation. These observations imply that rupture of the follicle and discharge of the ovum under ordinary circumstances is, in this animal, the result of a hormonal influence of some sort exerted by the pituitary. Liberation of the hormone responsible for the effect apparently occurs within one hour after copulation. Smith, however, does not believe that any specific "ovulation hormone" exists, but that ovulation is the result of a balance struck between the follicle-stimulating and the luteinizing hormones. Afferent impulses from the genital tract are apparently responsible, in part, for the liberation during coitus of the pituitary principle causing ovulation, but they are not essential, for Fee and Parks have shown that ovulation occurs after the vulva and vagina have been anesthetized. Sexual excitement resulting in an orgasm is capable alone (i.e., without coitus) of causing ovulation in the rabbit. That the influence upon the pituitary in this instance is of central origin is indicated by the observation that ovulation may be induced in the rabbit by electrical stimulation of the cerebrum or lumbosacral cord

(Marshall and Verney), or by the intravenous injection of the convulsant drug picrotoxin. Ovulation can also be induced by stimulation of the cervical sympathetic, the hypothalamus, the hypothalamo-hypophyseal tract of nerve fibers or of the pituitary itself.

The ovulation response is abolished with difficulty for impulses reaching the pituitary from many sources are capable of inducing it. Brooks found that it was not prevented after coitus though the sacral spinal cord, both sympathetic chains and the uterus, together with the proximal half of the vagina had been removed. Nor is it abolished by ablation of the neocortex and olfactory lobes. It no longer occurs, however, after section of the pituitary stalk. It is also abolished in animals whose hind limbs have been paralyzed by section of the lumbar spinal cord. Sexual excitement aroused by proprioceptive and tactile impulses from the limbs as the animal accommodates its posture during the act of copulation appears to be an indispensable factor in the response. The conclusion to be drawn from these various types of experiment is that though genital stimulations may elicit the response, they are not essential. On the other hand, the cooperation of the animal in the act of coitus and the associated sexual excitement appear to be necessary factors. If impulses reach the pituitary along the hypothalamo-hypophyseal tract of nerve fibers.

The following is a summary of the pituitary influence upon the sex mechanism. The follicle-stimulating principle initiates sexual activity. The ovaries or testes, stimulated by this anterior lobe hormone, bring about the psychic phenomena of puberty and of the estrous cycles of postpubertal life, as well as the physical changes in the accessory organs (vagina, uterus and seminiferous vesicles) characteristic of the sexually mature animal. It stimulates the development of the ova and granulosa cells of the follicles and, in the male, the epithelium of the seminiferous tubules. The luteinizing hormone depresses the first part of the ovarian cycle and encourages the second luteal phase, thereby bringing about the uterine changes associated with pseudo-pregnancy or with gestation. It acts specifically upon the cells of the theca and granulosa with the production of progesterone, or, in the case of the male, upon the interstitial cells of the testes with the production of male hormone.

The basophil cells (p. 722) are probably the source of the gonad-stimulating hormones; after castration the basophil elements of the anterior pituitary of the rat are increased in number and size ("castration cells"¹¹) while the gland's content

¹¹ These structures contain a large vacuole, the latter by pushing the nucleus toward the circumference of the cell gives it an appearance resembling that of a signet ring.

¹⁰ Smith suggests that since this principle stimulates the germinal tissue of both sexes it be called the *gametokinetic hormone*.

in gonadotropic principles increases. Moreover, when a castrated male rat and an hypophysectomized female are united parabiotically the female enters into continuous estrus and its ovaries show large numbers of follicles (superovulation). These results indicate that the relationship between the pituitary and the gonad is not one-sided but that the latter exerts, normally, a restraining influence upon the gonadotropic functions of the former. Such a relationship is supported by the converse observation, that continued treatment with estrin reduces the gonad-stimulating power of the anterior pituitary, the ovaries showing atrophic changes. The changes in the anterior lobe induced by estrin injections are, increased vascularity, reduction in number and ultimate disappearance of basophil and acidophil cells with proportionate increase in chromophobes. It is considered probable that the sequence of the two phases of the ovarian cycle is governed through the interplay of ovarian and pituitary hormones. Then, for example, as a result of follicular stimulation the estrin concentration in the blood reaches a certain level the liberation of the follicle-stimulating hormone of the anterior pituitary is suppressed and the discharge of luteinizing hormone brought about.

The Aschheim-Zondek test for pregnancy

The experiments of Aschheim and Zondek have led to the development of a practical test for pregnancy. After the injection of 2 cc. of urine of a pregnant woman (divided into 6 doses given over a 2-day period) into an immature male mouse 3 to 4 weeks old, the following ovarian changes are produced.

- (1) Ripening of follicles and estrus.
 - (2) Hemorrhages into some unruptured follicles, giving rise to "blood spots" (Blutpunkte) about the size of a pin's head.
 - (3) Luteinization of follicles in which the ova are retained—atretic corpora lutea.
- Effects (2) and (3) appear usually within 100 hours and permit a diagnosis of pregnancy to be made. Reaction (1) is not entirely specific since it occurs in conditions other than pregnancy, e.g., at the menopause (p. 762) and in new growths of the genital organs (see p. 758), especially teratoma. The test gives a correct result (positive or negative) in nearly 99 per cent of cases. A diagnosis of pregnancy as early as the first day after the first missed menstrual period

Estrin does not appear in large amounts in the urine until a much later date and small amounts are present

can be made by the use of this test.¹² The test fails in lower animals (e.g., rat, dog, cat, etc.) and the monkey, but is positive in the chimpanzee.

The test depends upon the presence of living placental (chorionic) tissue. Consequently a positive result is obtained when such abnormalities of gestation such as tubal pregnancy, hydatidiform mole or chorion-epithelioma exist. In the latter two conditions unusually large amounts of the gonadotropic principle are present in the urine. The test is also positive in threatened abortion but becomes negative when detachment and death of the ovum occur. Metastatic tumors of chorionepithelioma cause a positive reaction after removal of the uterus; the test may therefore prove invaluable as an aid in the diagnosis of the dissemination of this malignant disease. In the male, testicular tumors composed of malignant embryonal tissue (teratoma, epithelioma) also cause a positive test; such growths may result in the appearance of relatively enormous amounts of gonadotropic substance in the urine. Many cases of pituitary tumor give a positive test.

Friedman has modified the foregoing technique by substituting rabbits for mice as test animals. Since rabbits, ordinarily, ovulate only after sexual excitement, adult animals may be used for the test. This is a distinct advantage, as is also the fact that the ovarian reaction is developed much earlier—within from 16 to 36 hours (fig. 307). The animals must have been isolated from the males for at least three weeks prior to their use in order to ensure that natural ovulation has not occurred. Five to 10 cc. of pregnancy urine are given in a single intravenous injection. The percentage of correct diagnoses is about the same as when immature mice are employed.

The excretion of gonadotropic hormones in the urine

It has been assumed that the gonadotropic effects of pregnancy urine discovered by Aschheim and Zondek were due to the gonad-stimulating hormones of the pituitary; these, it was supposed, were elaborated in greater amounts during pregnancy than at other times, the excess being eliminated by the kidney. As a result of later work it is now generally agreed that the follicle-

in the urine of non-pregnant women. Aschheim states that the diagnosis of pregnancy by means of the urine is a very ancient practice. In an Egyptian papyrus some 3000 or 4000 years old it is directed that should a woman wish to know whether or not she is pregnant she should place some earth and barley in a vessel and add a little of her urine each day. Should the barley grow she is pregnant. It may be remarked that estrin, which as already mentioned, is present in high concentration in the urine after the first month or two of pregnancy, is a stimulant to plant growth.

stimulating and luteinizing effects of pregnancy urine are not due to the pituitary hormones but depend upon a *single* substance of a different nature. Pregnancy urine, for example, unlike anterior lobe transplants, will not stimulate follicular maturation or luteinization in the intact monkey nor in puppies or rats after hypophysectomy. Furthermore, reagents which are effective in extracting the urinary principle do not yield active extracts from the pituitary. The active principle in pregnancy urine is now referred to by some authors as *prolan*. This term tends, however, to perpetuate the confusion concerning

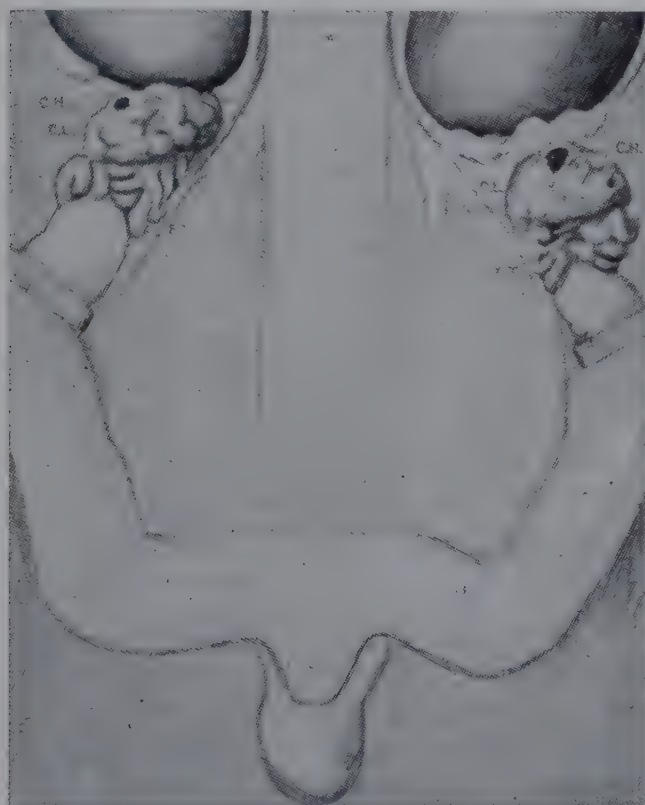


FIG. 307. Genital tract of mouse treated with urine of pregnancy. O, ovary; C.H., corpus hemorrhagicum; C.L., corpus luteum; F.T., Fallopian tube; U., uterus; V., vagina; (after Ettinger, Smith and McHenry).

the nature of the active principle in pregnancy urine. Collip and his associates have shown the latter to be identical with the gonadotropic substance of the placenta, and have named it the *anterior-pituitary-like substance* (A.P.L.) (see below). It is now more commonly spoken of as *chorionic gonadotropin*.

On the other hand, a hormone identical with the follicle-stimulating hormone of the pituitary and apparently elaborated by the latter is present in the urine of *castrated* animals and men, in the urine of pregnant mares and in the urine of women after the *menopause* or following *ovariectomy*. Its appearance in the urine may also be associated with *new growths* of the generative organs (both

benign and malignant but especially the latter), and with *raised intracranial pressure*. Occasionally it is found in the urine of normal men or of non-pregnant women before the menopause. This principle, unlike that in pregnancy urine, is effective when tested upon normal monkeys or hypophysectomized rats.

PLACENTAL HORMONES

The human placenta contains (a) the two forms of estrin;—*estrone* (ketohydroxyestrin or theelin, p. 749) and *estriol* (trihydroxyestrin or theelol); and (b) the *anterior-pituitary-like substance* or *chorionic gonadotropin* mentioned above. This ovary-stimulating principle has an action similar to but not identical with the gonadotropic principles of the anterior pituitary. Weisner extracted placental tissue with sulphosalicylic acid and obtained a gonadotropic substance which he believed consisted of two separate hormones—follicle-stimulating and luteinizing—identical with the gonadotropic hormones of the pituitary. He referred to them as rho I and rho II, terms which correspond to the names prolan A and prolan B used by Aschheim and Zondek. Collip, employing acetone as an extracting agent, obtained the ovary-stimulating principle but believed it to be a single hormone and showed that its physiological properties differed in certain respects from those of the pituitary hormones, hence the designation “anterior-pituitary-like.”

SUMMARY OF SOME OF THE MORE IMPORTANT OBSERVATIONS RELATING TO THE NATURE AND ORIGIN OF THE GONADOTROPIC PRINCIPLE OF PLACENTA AND PREGNANCY URINE, CHORIONIC GONADOTROPIN (URINARY PROLAN)

(1) When sexually immature rats, about 20 days old, are treated with A.P.L., prepared from the placenta or with extracts of pregnancy urine follicular maturation and estrus are induced; true corpora lutea are formed. The luteinizing effect predominates. The ovaries become enlarged, but the enlargement is somewhat less than that induced by anterior lobe extracts or implants. The ovarian effects of the urinary principle do not increase in proportion to the dosage, whereas those of pituitary transplants or extracts increase in direct relation to the amount of tissue transplanted or to the dose of extract (Evans and Simpson). A.P.L. prepared from the placenta or the gonadotropic principle in pregnancy urine causes marked development of the mammary glands in virgin rats. Enlargement of the prostate and seminal vesicles, and to a less extent of the testes of normal immature rats and of adult rats, is produced. The germinal epithelium

the testes is stimulated. The principle in pregnancy urine, unlike anterior lobe extracts, exerts no effect on the immature testes of birds.

(2) The A.P.L. principle, though obtainable in relatively large amounts from human placental tissue, is absent from the placentae of lower mammals; the gonadotropic principle disappears rather promptly from the urine shortly after parturition, and it is not found in the urine during pregnancy of any animal below the higher apes, though the pregnant mare secretes a gonadotropic principle of pituitary origin in the first month or so of gestation.

(3) In chorionepithelioma, a malignant tumor of placental (chorionic) tissue, and hydatidiform mole, a cystic degenerative disease of chorionic tissue, A.P.L. is present in large amounts in the pathological tissue and "prolan" is in high concentration in the urine. The gonadotropic hormone is found in high concentration in the chorionic villi of even very young embryos. It also appears in the urine of males suffering from tumors containing chorionic tissue.

(4) Tests of the gonad-stimulating properties of anterior pituitary tissue of women dying during pregnancy indicate that the gonadotropic principles in the pituitary during pregnancy are in very much lower concentration than in the pituitaries of non-pregnant women, and may even be absent. The diminished production of gonadotropic hormones by the pituitary during pregnancy is probably the result of the high concentration of estrin in the blood.

(5) Anterior lobe extracts will prevent ovarian atrophy in hypophysectomized animals, whereas the urinary principle exerts little or no protective action.

(6) Animals which have become resistant to the action of A.P.L. will still respond to anterior lobe extracts, and conversely those which have become resistant to the latter will respond to A.P.L.

The foregoing summary indicates that the A.P.L. substance of the placenta and the gonadotropic principle of pregnancy urine (prolan) are identical, i.e., the gonadotropic principle in the urine of pregnancy is derived, not from the pituitary but from the placental (chorionic) tissue. A possible function of the gonadotropin of the placenta is that it serves to supplement the action of the pituitary in maintaining the growth of the corpus luteum during pregnancy. The low concentration of gonadotropin in the pituitary of pregnancy conforms with such a possibility. According to this, if the placenta furnishes a hormone which, acting through the mediation of the ovary (corpus luteum), ensures its own physiological integrity, then a hormone liberated by the body of the embryo itself is not the factor which prevents regression of the corpus luteum as indicated by the results of an experiment of Collip, Selye and Thomson. They removed the embryos by Cae-

sarean section from rats between the ninth and thirteenth days of gestation, leaving the placentae intact. In a succeeding period of from eight to twelve days the corpora lutea remained unchanged, the placentae lived and the uterine mucosa between the placentae showed varying degrees of activity characteristic of this period of the pregnant state.

Is corpus luteum hormone formed by the placenta?

Though in some species, such as the rat, the corpus luteum persists to the end of pregnancy, in others, including the human, it commences to degenerate some weeks before term. In the rat and rabbit, abortion occurs if the corpora lutea are destroyed, whereas in the human and other species in which regression of the corpus luteum occurs, ovariectomy may be performed in the later part of pregnancy, though not during the earlier part, without abortion resulting. Even in the rat, though the embryos die after ovariectomy as a result of the uterus contracting upon them, and changes occur in the uterine mucosa, the placentae survive. Furthermore, if all the fetuses except one are removed from a pregnant rat, but *all* the placentae retained, removal of the ovaries after the middle of pregnancy does not cause abortion of the single fetus (Haterius). These facts have suggested the possibility that some tissue developed during the pregnant state—placenta or embryo—manufactures corpus luteum hormone. Some workers have prepared extracts from placental tissue which were capable of producing progestational changes in the uterus of the immature rabbit. The experimental results of Collip and his colleagues also give strong support to this view of placental function. They removed the *ovaries and embryos* from rats about the middle of pregnancy leaving the placentae undisturbed; the latter remained alive and apparently in a normal state during a subsequent period of from 5 to 9 days. The endometrium showed the normal gestational state; the mammary glands were well-developed, but did not secrete. From this and the experiment cited in the preceding section it is evident that the embryo does not elaborate a hormone which is concerned either indirectly through the luteal tissue of the ovary, or directly, with the maintenance of the placenta. Both these functions are probably performed by the placenta during the later weeks of pregnancy. Belief in the placental origin of the corpus luteum hormone is strengthened by the observation that the reduction product of progesterone, namely

pregnandiol, continues to be excreted in the urine following destruction of the corpus luteum in the later months of pregnancy.

THE MENSTRUAL CYCLE

UTERINE CHANGES

In primates (man, anthropoid apes and higher monkeys) the reproductive organs pass through a series of changes at periodic intervals. This constitutes the menstrual cycle. The most evident phenomenon of the cycle is the escape of blood from the vagina. The hemorrhage has its origin in the endometrium and is called *menstruation*.

Markee has followed the process of menstruation microscopically in patches of endometrium transplanted into the anterior chamber of the eyes of monkeys. Bleeding occurred from the transplanted tissue during menstruation, but preceded the appearance of blood in the vagina by about 3 hours. Estrin injections produced dilatation of the vessels of the graft. These observations emphasize the essentially endocrine nature of the uterine changes occurring during the menstrual cycle. In the human subject patches or tumors of endometrial tissue are sometimes found in extra-uterine situations, e.g., surface of the broad ligament or ovary; in the omentum, pelvic peritoneum or subcutaneous tissue of the vulva or perineum, or in the tissue in the neighborhood of a laparotomy scar. The ectopic tissue bleeds during menstruation and may give rise to attacks of severe pain. The condition is not very uncommon. It is referred to as *endometriosis*.

It is generally believed that rhythmical variations in the activity of the anterior pituitary are primarily responsible for the regular recurrence of the menstrual cycle, the ovary (through the discharge of estrin and progesterin) playing the rôle of intermediary. Menstruation is the most obvious event in the menstrual cycle and is customarily described as the first stage, but actually it is the culminating stage. It will therefore be placed last in the following division of the cycle. This order is also more convenient in correlating the ovarian cycle with the uterine changes.

(1) The *stage of repair and proliferation—follicular phase*. During this stage the epithelium of the endometrium which was shed during the menstrual flow is restored. The uterus enlarges as a result of the growth of its stroma; it becomes more vascular, its arteries become coiled, the epithelial lining hypertrophies and the glands show proliferative changes. Ovulation occurs at about the end of the proliferative stage which therefore

corresponds to pro-estrus of animals. The uterine changes are dependent upon the action of the follicular hormone (estrin).

(2) The *premenstrual or secretory stage—luteal phase*. This stage commences from 12 to 14 days before the first day of the menstrual flow. The uterine mucosa shows marked hypertrophy, glands become elongated and assume a coiled corkscrew form. The glandular secretion becomes greatly increased and more mucoid in character. This stage is dependent upon the action of the corpus luteum; it corresponds to pseudo-pregnancy of certain animals. Toward the end of the premenstrual stage the endometrium resembles the decidua of early pregnancy, typical decidua capsularis appearing in the uterine stroma. Toward the end of the follicular phase the vessels of the mucosa constrict. Swelling of the mammary glands and often mild psychic disturbances (irritability, nervousness, depression, etc.) occur. This stage may be absent from the menstrual cycle (p. 761).

(3) The *destructive stage or stage of menstruation*. This stage of menstruation lasts for about four days. The vasoconstriction toward the end of the follicular phase and the resulting ischemia of the endometrium lead to necrosis of the superficial layers; dilatation of the vessels then ensues accompanied by shedding of the necrosed tissue and bleeding from the denuded surface.

Menstrual blood as it appears externally is incoagulable. This is probably due to its containing a substance (fibrinolysin) which has destroyed the fibrin in the clots previously formed in the uterus or vagina.

OVARIAN CHANGES

The uterine changes are associated with just definite changes in the ovary. During the stage of proliferation of the endometrium the Graafian follicle is undergoing maturation. Ovulation occurs around the 15th day (13th to 17th) after the first day of the last menstruation, that is, about mid-way between two menstrual bleedings or "periods", and, as already mentioned, at about the end of the proliferative stage. Corner has recovered unfertilized ova at this time from the Fallopian tubes of monkeys, and Newell, Allen, Pratt and Bland, from the tubes of women. During the endometrial hyperplasia of the premenstrual stage the corpus luteum is developing. It reaches its maximal size at the end of this period if fertilization of the ovum does not occur, and its subsequent degeneration coincides with the onset of the menstrual flow.

of the menstrual flow (figs. 306 and 308). If fertilization and successful implantation of the ovum occur the corpus luteum continues to enlarge (p. 751). The excision of a recently formed corpus luteum is followed by menstruation or, if implantation of the ovum has occurred, by abortion.

Ovulation is accompanied by a sharp rise in electrical potential between the uterine cervix and the abdominal wall. This phenomenon was first demonstrated in the rabbit by Burr and his associates in 1935 and has since been fully confirmed by others. The potential change amounts to from 6 to 10 microvolts and lasts for about an hour. It is detected by means of electrodes placed in the situations mentioned, and connected to a sensitive potentiometer which activates a moving-cell galvanometer. The potential change can be recorded photographically. This method has been employed to ascertain the time of ovulation in women, the electrical change having been correlated with the presence of a recently ruptured follicle in the ovary.

Ovulation is also followed by the appearance of pregnandiol in the urine (p. 753). The detection of this derivative of progesterone is therefore taken as evidence of ovulation and fixes approximately the time of its occurrence.

It would seem that the menstrual rhythm once initiated is perpetuated automatically through the interaction of the pituitary and ovary. From the facts in hand it is possible to draw tentatively the following picture of the governing mechanism. Estrin increases in the body fluids, due to stimulation of the ovary by the follicle-stimulating hormone of the pituitary, but when the concentration of this ovarian hormone reaches a certain level it acts in turn to suppress the output of the follicle stimulating hormone; the concentration of estrin upon which the proliferative stage of menstruation depends is thus reduced. The hypophysis now releases its luteinizing principle which stimulates the development of the corpus luteum, but as the concentration of progesterone rises the production of the luteinizing principle is in turn suppressed, with the result that the integrity of the luteal tissue cannot be maintained. The concentration of estrin having by this time fallen to a low value, menstrual bleeding occurs and the secretion of follicle-stimulating hormone is then resumed—another cycle commences. There is evidence that the liberation of the gonadotropins of the pituitary is under the control of the hypothalamus.

A CONSIDERATION OF THE FACTORS CONCERNED IN THE PRODUCTION OF THE MENSTRUAL FLOW

Hartman's studies have shown beyond doubt that menstruation occurs without ovulation in the monkey, especially between mating seasons. Menstruation without ovulation also occasionally occurs in women. A corpus luteum of course is not formed in these instances and the typical premenstrual endometrial changes do not occur. It appears, therefore, that, though the breakdown of a premenstrual endometrium built up under the influence of the luteal hormone ordinarily coincides with the menstrual flow and is normally part of the mechanism, it is not an essential feature. On the other hand, estrin and the endometrial changes which it brings about are an indispensable part of the menstrual process.

Certain observations indicate that an important factor in the onset of menstruation is an abrupt fall in the estrin concentration of the blood. (a) In monkeys, and also in the human subject ovariectomy (which removes the source of estrin) is followed by uterine bleeding. This postoperative bleeding may be postponed by injections of estrin. (b) When a castrated monkey is given a series of injections of estrin, uterine bleeding occurs a few days after the cessation of the treatment but unless the injections are long continued no bleeding occurs during the course of the treatment. The same phenomenon has been observed in women. Progestin injections prevent the effect of the estrin treatment. (c) In non-pregnant women the maximum excretion of estrin occurs in the intermenstrual period, and the minimum just before or at the time of menstruation. (d) Injections of a gonadotropic extract of the anterior lobe of the pituitary into a monkey during the resting stage of the cycle causes bleeding a few days after the treatment has been discontinued. This result, since it cannot be produced after ovariectomy, is apparently due to estrin liberation and a rise followed by a fall in the estrin concentration of the blood. If the treatment with pituitary extract is followed by injections of estrin, menstruation is postponed until a week or so after the latter treatment has been discontinued.

To summarize: Menstruation can occur in the absence of ovulation; the premenstrual endometrium characteristic of the action of the luteal hormone is therefore not necessary for its occurrence. Stimulation of the endometrium by estrin is, however, absolutely essential, and a reduction

in the concentration of estrin in the blood appears to be the chief factor in the onset of the bleeding.

ATTEMPTS TO IDENTIFY MENSTRUAL BLEEDING WITH ONE OR OTHER PHASE OF THE ESTRUS CYCLE OF LOWER ANIMALS

The menstrual cycle of primates is homologous with the estrous cycles of animals (expressed in terms of lower animals, the human is polyestrous (p. 746)), but to what stage of the estrous cycle menstrual bleeding itself corresponds is a debatable question. In animals such as the dog and cow bleeding occurs in pro-estrus. This led Heap to suppose that menstruation was homologous with pro-estrous bleeding. But whereas the proliferative phase of the menstrual cycle corresponds apparently to pro-estrus in animals, menstruation does not occur until some 14 days after the termination of the proliferative phase (cf. fig. 308).

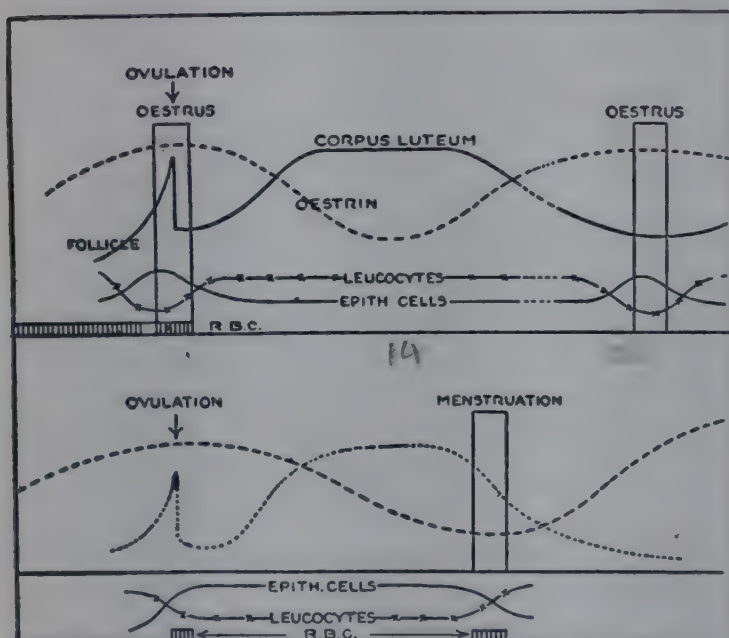


FIG. 308. Upper diagram, oestrous cycle. Lower, menstrual cycle. (After Corner.)

It has been mentioned that the premenstrual changes in the uterus resemble and are considered to correspond to those of pseudo-pregnancy in animals. Parkes and Bellerby have therefore suggested that menstruation is the homologue of the slight bleeding which occurs in some animals as the uterine mucosa breaks down at the end of pseudopregnancy. Color has been given to this theory by the fact that uterine bleeding promptly ensues after destruction of the corpus luteum. It has just been stated, however, that menstruation can occur in the absence of a luteal phase.

Marshall has suggested that menstruation corresponds to the hemorrhage at the end of pseudo-pregnancy and the bleeding of the pro-estrus period of the next cycle "telescoped" into one. The difficulty in correlating menstruation with pro-estrus bleeding has been mentioned. Furthermore, slight bleeding sometimes occurs in women at about the *time of ovulation* (intermenstrual period) which would be more comparable than menstruation with pro-estrus bleeding.

Another theory (*embryotrophic hypothesis*) postulates that menstruation is homologous with the extravasation of blood into the decidual tissues which occurs during implantation of the ovum and serves to nourish the embryo in the initial stages of its development. Occasionally the extravasated blood escapes into the uterine cavity and appears externally (the so-called *placental sign*); a similar hemorrhagic discharge occurs in animals in a certain percentage of pseudopregnancies. This theory is in harmony with the common observation that in women bleeding may occur shortly after conception (i.e., during implantation of the ovum which is indistinguishable from that of an ordinary menstrual period. The theory is attractive in that it interprets menstruation as the culminating event in the preparation of the uterus for the reception of a fertilized ovum, the growth of the corpus luteum and the premenstrual changes in the uterine mucosa constitute the earlier preparatory processes projected in anticipation of implantation.

It must be admitted that none of the foregoing views succeeds in harmonizing all the facts.

PUBERTY AND THE MENOPAUSE

The sexual life of the human female commences between the 12th and 14th years, when the first menstruation or *menarche* occurs. This period of sex awakening which is seen in animals and men of both sexes is referred to as *puberty*. The periods before and after are called *pre-pubertal* and *postpubertal*, respectively. The ovaries at this time show increased growth accompanied by the maturation of the Graafian follicles and the discharge of ova. The growth of the uterus is accelerated, the breasts enlarge and, in both girls and boys, hair appears up on the pubes and in the axillae. Deepening of the voice, enlargement of the genitalia (penis and testes), increased muscular development and growth of hair on the face are characteristic features of this period in boys. In both sexes, somatic growth, including the lungs, skeleton, kidneys and liver is accelerated.

Between the ages of 42 and 52 (average 47 years) the sexual processes come to an end. This time is spoken of as the menopause or climacteric. Menstruation ceases, retrogressive changes gradually supervene in the accessory organs of reproduction, e.g., atrophy of the uterus, shortening and narrowing of the vagina, loss of the pavement epithelium and its replacement by fibrous tissue and shrinkage of the mammary glands. The changes are the result of atrophic changes in the ovary—disappearance of the Graafian follicles together with a general fibrosis and shrinkage of the organ; similar changes in the uterus and vagina follow the removal of the ovaries in early

life—*artificial menopause*. Psychic phenomena, usually mild, are not infrequent accompaniments of the menopausal period. Occasionally serious mental disturbances, e.g., melancholia, appear at this time. Vasomotor disturbances, hot flushes, sweating, etc., are very common features of the climacteric. The effect of the natural menopause upon the sex libido varies in different subjects. In married women it shows little alteration as a rule. Estrin may be present in the blood and urine years after the onset of the menopause. The follicle-stimulating hormone of the pituitary appears in the urine after the cessation of the menses.

MENSTRUAL IRREGULARITIES

The non-occurrence of the menstrual periods in postpubertal life is called *amenorrhea*; except during pregnancy, when suppression of the menses is a physiological phenomenon, the failure of the menstrual cycles at any time between puberty and the menopause is abnormal. Amenorrhea may be either *primary* or *secondary*. In the former instance the menses have never occurred, in the latter they appeared but were subsequently suppressed. Primary amenorrhea is in many instances associated with arrested development of the reproductive organs. Scanty menstruation is termed *oligomenorrhea*. *Dysmenorrhea* is painful menstruation. *Menorrhagia* is the term applied to excessive loss of menstrual blood. *Metrorrhagia* is the loss of blood from the uterus in the intermenstrual periods. A large proportion of these menstrual irregularities, when unaccompanied by some gross disease (tumor, etc.) in the uterus, have an endocrine basis. Amenorrhea is frequently the result of ovarian hypofunction. Dysmenorrhea is the result of irregular and spasmodic contractions of the uterine muscle which probably have also in many cases a hormonal origin. In the past, excessive bleeding in the absence of some obvious uterine disease has been put down to inflammation of the uterine mucosa (endometritis). Before the important work of Hitschmann and Adler, who correlated the physiological changes in the endometrium with the stages of the ovarian cycle (p. 760), the normal premenstrual characters of the uterine mucosa were considered to be pathological—evidence of endometritis!

Shaw, from the study of a large series of irregular uterine bleedings unaccompanied by obvious disease of the uterus, came to the conclusion that only a very few could be attributed to inflamma-

tory changes in the endometrium but that the great majority were due to ovarian abnormalities. In one group (*metropathia hemorrhagica*) the bleeding was continuous, the uterine mucosa was thickened and showed dilated glands and areas of necrosis; the constant finding in the ovary was an unruptured cystic follicle. The bleeding is apparently due to the overproduction of follicular hormone and the prevention of the formation of a corpus luteum. According to Kaufmann the imbalance between these hormones causes the proliferative phase of the endometrium (p. 760) to become exaggerated, and prevents the onset of the secretory phase and the shedding of the mucosa as in normal menstruation. He describes the state of the endometrium as one of chronic cystic hyperplasia. This observer has produced a similar state of the endometrium in a castrated woman by the administration of large doses of follicular hormone.

In another group of cases of uterine bleeding reported by Shaw (*epimenorrhea*) the menstrual flow was prolonged, that is, the intermenstrual periods were much shortened; the ovarian cycles, due to premature rupture of the follicles, were also abbreviated, ovulation occurring with abnormal frequency.

In cases of irregular uterine bleeding of endocrine origin the ovarian disorders are possibly due in turn to disturbances of a functional nature of the anterior lobe of the pituitary. It is well known that gross diseases of this part of the pituitary (e.g., acromegaly, Simmonds disease, dystrophia adiposo-genitalis, pituitary basophilism, etc.) are associated with menstrual abnormalities. These, however, usually take the form of oligomenorrhea or amenorrhea. Amenorrhea also occurs as an accompaniment of hypothyroidism and as a symptom of several general diseases, notably anemia, tuberculosis and mental conditions; malnutrition is not infrequently a cause.

The *treatment* of menstrual disorders, supposedly of ovarian origin, by means of hormone preparations has been very disappointing, and this is perhaps to be expected until a clearer understanding of the underlying factors governing normal menstruation has been arrived at. Estradiol dipropionate or benzoate has been employed with some measure of success in secondary amenorrhea, especially if this has not been of long standing. Primary amenorrhea is not permanently benefited by the follicular hormone. Werner and Collin produced uterine bleeding in castrated women by the administration of estrin alone, but

the premenstrual type of endometrium was not produced. Treatment of primary amenorrhea with estrin and progestin together would appear to have a more rational basis and might be expected to give better results, for, though the progestational development of the uterine mucosa is not essential for menstruation (p. 761) this *does* occur in the normal subject. Yet even this mode of treatment is on the whole unsatisfactory. Kaufmann produced typical premenstrual endometrium in castrated women by the administration of the two ovarian hormones, but a total dose of over 1,000,000 international units of estrogenic principle (progynon) and 35 rabbit units of corpus luteum hormone were required to produce this effect. He also induced growth of the uterus and uterine bleeding in cases of primary amenorrhea associated with genital infantilism by the administration of enormous doses of estrin (up to 18,000,000 international units over a period of months) or of this hormone followed by injections of the corpus luteum principle. A premenstrual endometrium was not produced in these cases and the bleeding was therefore not considered to be normal menstruation. In cases of primary amenorrhea with well developed genitalia, a typical premenstrual endometrium followed by menstruation was induced by the administration of a total dose of from 1,000,000 to 1,500,000 international units of follicular hormone and from 35 to 50 rabbit units of corpus luteum hormone. In no case of primary amenorrhea of the first group and in only one case of the second, however, was a cure brought about, in the sense that normally recurring menstrual cycles occurred; after the course of treatment, the subjects in all the other instances relapsed into their previous amenorrheic condition. Such a result is to be expected, since the administration of ovarian hormones cannot correct the primary fault whether this be of ovarian or pituitary origin. In a number of cases of secondary amenorrhea, on the other hand, the spontaneous cyclic function of the uterus was restored by treatment with both hormones or with large doses of estrin alone.

Estriol, stilbestrol or emmenin, since they are more effective by oral administration than estrone, and therefore more convenient, are often used in its stead.

The greatest value of estrone or of the other estrogens is in the treatment of the nervous (psychic and vasomotor) disturbances of the menopause in which the estrin concentration in the blood and urine is frequently definitely subnormal.

Injections of estrogens in such instances relieve the vasomotor symptoms. Relatively small doses (200 international units daily) are required. Estrone has also been shown to be of definite value in the treatment of gonorrheal vulvovaginitis in children. Under its influence the vaginal epithelium undergoes cornification and, assuming the characteristics of the sexually mature woman, becomes more resistant to the disease. Estrone has also been employed with success in intractable cases of pruritis vulvae, and in certain ulcerative conditions of the vaginal mucosa.

Not until recently has an active preparation of progestin suitable for clinical use become available. Preparations previously on the market and claiming to contain the corpus luteum hormone were inert; this also applies to some of the preparations which are offered today. We have seen (p. 751) that the changes in the uterine mucosa which are essential to the fixation and nourishment of the fertilized ovum are dependent upon the hormone of the corpus luteum. Deficiency of the latter may be responsible for certain cases of sterility or of habitual abortion, and when such a cause is suspected, treatment with an active preparation (which must always be given by injection) is a rational procedure. The indication for the use of progestin in menstrual disorders is by no means clear cut. Its inhibitory effect upon uterine motility renders it a valuable agent in the treatment of dysmenorrhea; and its action in suppressing the menstrual flow has been the basis for its use in menorrhagia and metrorrhagia. Excellent results have been reported following its use in the latter conditions. Kaufmann found that up to 90 rabbit units of corpus luteum hormone were necessary in order to suppress the proliferative phase (p. 760) of the endometrium and bring on the secretory phase. Smaller doses, however, were frequently successful in terminating the bleeding. Progestin is of no value in the treatment of the symptoms of the menopause.

A.P.L. from pregnancy urine has also been advocated where treatment with corpus luteum hormone appeared to be indicated; the object being to stimulate luteinization and so to increase the subject's own supply of hormone. There is no evidence, however, that in the human subject A.P.L. causes luteinization; it has not this effect in the ape. Nevertheless, Campbell has reported success in the treatment of metropathia hemorrhagica with A.P.L. hormone. Novak and Hulse also report success in the treatment of menorrhagia with the anterior-pituitary-like principle. The

rationale of its action in these instances is obscure. Testosterone propionate (p. 771) has also been employed with satisfactory results.

The naso-genital relationship. A number of observations suggest a physiological relationship between the sex processes and the nose. In the first place the mucosa covering the conchae has a cavernous structure suggestive of the erectile tissue of the penis and clitoris, and olfactory stimuli and psychic aspects of sex are very closely associated. Nasal congestion, often accompanied by epistaxis, occurs regularly in many women at the time of the menses and in both sexes it is not unusual for nasal bleeding to occur at puberty. Sometimes the nasal hemorrhage in girls or women has seemed to replace menstruation which was coincidentally suppressed, and for this reason was termed erroneously "*vicarious menstruation*." Swelling and reddening of the nasal mucosa is a common finding in women during pregnancy and in monkeys during the estrous cycles. Stimulation of the interior of the nose has been reported to alter the periodicity of estrous cycles in rats, whereas excision of the conchae in young animals is said to result in hypoplasia of the sex organs. On the other hand, degenerative changes in the nasal mucosa have been observed as a sequence to castration, which could be reversed by estrin injections. Finally, pseudopregnancy has been induced in rats by the nasal application of a strong solution of silver nitrate and by removal of the sphenopalatine ganglion. Mortimer, Wright and Collip became interested in the nasogenital relationship from the study of a French Canadian family, all of whom (both parents and nine children) suffered from *atrophic rhinitis*. An examination of the cranial skiagrams of these subjects disclosed signs which were interpreted as indicative of pituitary abnormalities. The possibility of a causative connection between the pituitary (e.g., deficiency of gonadotropic principle) and the nasal disease suggested a trial of estrin for the treatment of the latter. The local application of the follicular hormone to the conchae of these patients and of a number of other subjects of atrophic rhinitis is stated to result in definite improvement.

THE DEVELOPMENT OF THE MAMMARY GLANDS AND THE SECRETION OF MILK

The rôles played by the ovaries and the anterior pituitary. Prolactin (synonyms: mammatropic, galactin, lactogenic hormone)

There are three phases in the development and activity of the mammary glands.

(a) The mammary growth which occurs in animals at puberty and at the commencement of subsequent estrus periods, is due, mainly, to estrin (p. 747). In monkeys, treatment with estrin will prevent the atrophy of the mammae

which otherwise follows castration. This ovarian hormone brings the mammary glands of the immature guinea pig to full development, promoting the growth of both the alveolo-lobular and duct systems as well as that of the epithelium of the nipple. In the monkey, growth of the alveolo-lobular system is also stimulated by estrin.

(b) The further enlargement of the mammary glands during pseudo-pregnancy and during the pregnant state is due to the growth of the corpus luteum. In most animals, although estrin can stimulate growth of the ducts, stroma and nipple, development of the alveolo-lobular system can not, as in the case of the guinea pig and monkey, be induced by the administration of the follicular hormone alone. It must be combined with or followed by progestin administration, which then induces growth of the alveolo-lobular system. The effect of the sex hormones upon mammary growth is enhanced by the administration of the thyroid hormone.

Undoubtedly, the development of the human mammae at puberty and their enlargement in the premenstrual periods and during gestation are also due to the influence of the ovarian hormones.

The researches of Turner and his colleagues, indicate that estrin and progestin exert their respective effects upon duct and alveolo-lobular growth, not directly, but through the intermediary of the pituitary. They postulate the existence of two pituitary hormones, *Mammogen I*, which induces duct growth and is liberated under the influence of estrin, and *Mammogen II*, which is controlled by progestin and stimulates the growth of the alveolo-lobular system. Estrin, it is thought also exerts a direct action upon the growth of the stroma of the mammae.

(c) The actual *secretion* of milk which occurs at the end of pregnancy is brought about through the pituitary. A lactogenic effect of anterior lobe extracts was demonstrated by Grueter and Stricker in 1929; and Corner in 1930 showed that injections of anterior lobe extract caused hypertrophy of mammary tissue and secretion of milk in ovariectomized virgin rabbits. The work of Riddell and his associates has demonstrated that the lactogenic effect is due to a separate hormone of the anterior hypophysis. These observers obtained extracts of the anterior lobe which had pronounced lactogenic effects but were practically free from thyrotropic, growth and gonadotropic principles. They named the hormone *prolactin*. It has since been obtained in crystalline form, and in the form of what appears, from electrophoretic and diffusion

studies, to be a pure protein. It is most probably a product of the acidophil cells.

Prolactin induces proliferation of the epithelium lining the crop glands of male and female pigeons and doves,¹² and increases the production of a caseous material, consisting of desquamated epithelial cells and known as "crop milk," with which the young are fed. The epithelium becomes heaped up into a number of layers, producing pronounced thickening of the mucosa, an effect which is strikingly evident even upon gross inspection. Great numbers of mitotic figures appear. The stimulant action upon epithelial hyperplasia is greatly magnified by the administration of colchicine, a drug which arrests mitosis in the metaphase stage. The maximum effect of the drug is manifested in from 6 to 8 hours and persists for a period of from 16 to 18 hours. The lactogenic hormone causes the mammary secretion in all species of mammals investigated. On the other hand, hypophysectomy suppresses milk secretion; and in the cat, though pregnancy is not terminated by hypophysectomy performed in the later months, lactation does not occur postpartum in the absence of the pituitary. Prolactin arouses the maternal instinct in virgin rats; Riddle and his associates have shown that in from 5 to 12 days after a series of injections the treated animals will care for young. It also induces broodiness in hens. Continued injections suppress the gonadotropic action of the hypophysis with consequent atrophy of the gonads. In pigeons prolactin manifests a growth effect upon the body as a whole, but especially upon the liver and intestines and probably upon the pancreas (splanchnomegaly).

That milk secretion in the human subject is also under the control of the anterior lobe is indicated by the fact that in acromegaly (p. 736) milk secretion may persist for an extraordinarily long time after childbirth (5 years in a case of Cushing's). It may also occur in male subjects of giantism (p. 737). These observations are most readily explained upon the assumption that in these pituitary abnormalities the overactivity of the anterior lobe causes, as well as an overproduction of growth hormone, a continuous secretion of prolactin, corticotropin and possibly other lactogenic principles. Prolactin preparations have been used clinically to increase the milk flow. Riddle and his associates report that in a series of

twenty-nine parturient women the daily milk secretion was increased in twenty-five of them from 50 to 400 grams in from three to nine days after treatment was instituted.

A CONSIDERATION OF FACTORS CONCERNED IN THE INITIATION OF THE MECHANISMS LEADING TO MILK SECRETION AT THE TERMINATION OF PREGNANCY

Though, as mentioned above, in most animals as well as in the human subject, mammary growth occurs during pregnancy, the flow of milk is not established until after the birth of the young and the expulsion of the placenta. Complete information concerning the factors which initiate the secretion after the birth of the child is not available; though the importance of prolactin in the secretion of milk has been proved, the influences determining its discharge from the pituitary and the part played by other hormones are, to a large extent, unknown. Experimental results relating to the factors concerned in the induction of lactation—both hormonal and nervous—will be briefly outlined.

HORMONAL. (1) When mammary growth is induced in the guinea-pig by the injection of estrin, secretion of milk occurs when the dosage of hormone is suddenly reduced. (2) Evans found that "prolan" (which induces luteinization of the ovary, p. 755) caused mammary development in virgin rats but not the secretion of milk. Collip and his colleagues reported that if in virgin rats the luteinized ovaries induced by the administration of A.P.L. were removed, the hypertrophied mammae secreted profusely. Removal of the pituitary, however, together with the ovaries prevented this result. (4) Lactation is inhibited by estrin injections or by measures which stimulate estrin liberation; it is also promptly suppressed by injections of A.P.L. hormone which stimulate the production of luteal tissue. (5) The mammary glands of women who have been ovariectomized during pregnancy do not secrete unless abortion occurs and the placentae are expelled. (6) When lactating cows become pregnant, milk production declines progressively throughout gestation and rises again abruptly after calving. (7) It has been reported that reduction in the estrin concentration of the blood of parturient women, may be induced by the administration of a diuretic such as theophyllin, stimulates milk secretion. These are among the observations which have suggested to many that in the intact animal lactation is held in abeyance by a high concentration in the blood of ovarian hormones (estrin).

¹² This action is employed as a means of assaying the potency of lactogenic extracts. In general terms a "bird unit" is the minimal quantity of extract required to induce a certain increase in weight of the crop glands of doves or pigeons.

gestin) and probably of placental hormones as well, but that with the fall in concentration of these hormones toward the end of pregnancy, or at partum the pituitary and the adrenal cortex (see below), now no longer restrained, exert their trophic action. Evans also explains the milk secretion which occasionally occurs in the child shortly after birth (witch's milk) on this basis. The blood of the fetus presumably contains ovarian hormones of the mother and the elimination of these after birth results in the liberation of prolactin from the infant's pituitary. The theory just outlined concerning the induction of lactation fails to explain the phenomenon in all species. In some cases, continued administration of estrin actually stimulates mammary secretion. The embryo itself does not apparently elaborate a hormone which stimulates mammary growth during pregnancy which inhibits the secretion of milk (see p. 9).

The lactogenic hormone apparently acts directly on mammary tissue, rather than through the intermediary of some other endocrine, for it is effective when injected into the mammary ducts. Nevertheless, the hormones of the thyroid and adrenal exert an influence upon lactation.

In milking cows, thyroidectomy causes a slight reduction in the quantity of milk and a more pronounced reduction in the yield of butter fat (Hraham). The administration of the thyroid principle or of iodinated casein increases the yield of milk as well as the fat content. These effects appear to be specific and not due simply to changes in metabolism, for raising the heat production 50 per cent or so above normal by means of dinitrophenol decreases both the volume and the butter fat of the milk. The effect of thyroidectomy is attributed, in part, to the removal of the parathyroids.

The adrenal cortex plays an essential part in milk secretion. Rats, adrenalectomized in the later months of gestation fail to produce the normal quantity of milk. The defect can be corrected by the administration of very large doses of cortin, but not by ordinary (maintenance) doses, or by a high salt diet. The effect of adrenalectomy upon mammary secretion may be to a large extent non-specific and results from the disturbance in mineral, water and carbohydrate metabolism, the drying up of milk production being an expression of the dehydrated state. Nevertheless, that the adrenal cortex plays a rôle in milk-production is shown by the fact that prolactin alone has no trophic action in hypophysectomized animals unless an extract of the adrenal cortex (or cortico-

tropin) is administered with it. This leads to the belief that normally the pituitary brings about mammary secretion by liberating the adenotropic hormone as well as prolactin. Of the adrenal principles, desoxycorticosterone has been found to be without lactogenic action, whereas, 17-hydroxy-11-corticosterone is effective. The importance of the adrenal cortex in lactation and certain recent observations with the glycotrophic factor of the pituitary, as well as the influence of the ovarian hormones have led many, especially Folly and Young, to doubt the specificity of prolactin. The hormonal control of lactation is probably more complex than has been thought and involves perhaps several hormones.

NERVOUS. Cannon and his associates have shown that sympathectomized animals (cats) are in most instances unable to suckle their young (p. 945); a small quantity of milk is secreted after the young are born but the secretion soon dries up; maternal instinct is abolished. It is also well known that after weaning the secretion of milk ceases; there are two possible causes for this: (a) removal of the stimulus to the nipples provided by the act of suckling, or (b) distension of the alveoli of the gland by accumulated milk. Selye has shown that it is the first rather than the second of these factors which is important. The main duct of the gland was ligated in rats but the young were allowed to suckle. The accumulation of milk caused marked distension of the alveoli but secretion was not inhibited. On the other hand, removal of the sucklings from the mother or excision of the nipples suppressed secretion. It is probable that the effect upon mammary secretion of stimulating the nipple is not a local one but is the result of afferent impulses reaching the pituitary. Such a mechanism would be analogous to that by which in certain animals a pituitary principle, discharged as a result of stimulation of the genital tract, induces ovulation (p. 756). The experiments of Selye, Collip and Thomson indicate that afferent impulses from the uterus in a similar manner exert an important influence upon lactation. In the rat and other animals emptying the uterus by Caesarean section before term is followed by milk secretion. Selye and his associates found that secretion did not occur, however, if the uterus after evacuation was maintained in a distended state by means of injections of melted paraffin wax (with a melting point a little above body temperature). They conclude that the emptying of the uterus and the consequent reduction in tension upon the uterine wall is a factor in the response of

the pituitary. The inhibitory effect, however, may not be specific but due to the illness of the animals after the operation (see Bradbury, 1941; Greene, 1941).

The experiments cited above indicate the importance of *afferent* nervous influences in milk secretion, presumably through the liberation of prolactin. On the other hand, the fact that secretion may continue after complete denervation of the glands and that mammary tissue transplanted into a pregnant animal secretes milk after the young are born provides clear evidence that *efferent* nerves are not essential to the secretory mechanism, the *immediate* excitation of the gland being mainly brought about, if not entirely, by the lactogenic hormone of the pituitary.

The posterior lobe does not exert a true lactogenic effect, that is, it does not stimulate the *secretion* of milk by the mammary cells, but through its action upon the smooth muscle of the alveoli and ducts, pituitrin causes the expression of milk from the gland and in this way may temporarily increase the *flow* of milk; but the daily milk production is not increased.

THE COMPOSITION OF MILK

The quantity of protein in cow's milk is about double that in human milk, but the sugar and fat contents are lower. The proteins of human milk are, however, of higher biological value. In cow's milk casein constitutes from 80 to 90 per cent of the total protein, and lactalbumin from 10 to 20 per cent, whereas in human milk from 30 to 40 per cent of the total protein is lactalbumin. According to Murlin, all the protein of mother's milk may be retained by the infant; a considerable proportion of the protein of cow's milk, on the other hand, is eliminated.

The greater part of the fat of milk (90%) consists of the glycerides of the higher fatty acids, myristic, palmitic, stearic and oleic. The glycerides of lower fatty acids, butyric, caproic, caprylic, etc., make up the balance. Milk also contains small amounts of free fatty acids and of the phospholipids, lecithin, kephalin, and cholesterol. Cow's milk contains a relatively high percentage of inorganic constituents, the concentration of calcium being some three times, that of potassium twice, of sodium four times and of phosphorus over five times greater than in human milk. The calcium of human milk is said to be better utilized than that of cow's milk.

Both cow's milk and human milk vary greatly both in composition and quantity. Many factors,

psychic, dietary, period of lactation, time of day (greater volume during the night), etc., exert their effects upon the quality and quantity of human milk; the output gradually increases up to a maximum of from 1000 to 3000 cc. at about the 25th week after childbirth and then gradually declines. Human milk of good quality contains all the elements essential for building body tissue and adequate amounts of vitamins A, B complex and C. Vitamins B₁ and D are in low concentration and may be present in inadequate amounts. The average compositions of cow's milk and a woman's milk of good quality are compared in table 72. Both the *quality* and *quantity* of the milk is influenced by diet. An ample diet tends to maintain both the quality and quantity of milk at a high level. Raising the protein in the diet tends to increase the total milk yield. A high fat diet increases the yield as well as the fat content of the milk. A carbohydrate-rich diet reduces both the yield and the quality of the milk.

TABLE 72

	TOTAL PROTEIN	CASEIN	LACTAL- BUMIN	SUGAR	FAT	ASH
	per cent	per cent	per cent	per cent	per cent	per cent
Cow's milk..	3.5	3.0	0.5	5	3.5	0.7
Human milk.....	1.5	1.1	0.4	7	4.0	0.2

Milk is a true secretion—the product of the cells composing the alveoli of the mammary gland. The alveoli are grouped into lobules and the lobules into lobes. The secretion is collected by a system of intra- and inter-lobular ducts and delivered to the exterior by a single main duct, the galactophore—which opens upon the surface of the nipple.

The sugar of milk—lactose—is formed from the glucose of the blood. The protein is synthesized from free amino-acids; the phospholipids (lecithin, cephalin) are derived from the phospholipids of the blood. As a result of such conversions the concentrations of glucose, amino-acids and phospholipids is somewhat lower in the blood of the mammary vein than in that of the mammary artery. The origin of milk fat is an unsettled question.

THE TESTES

Structure of the testes

The substance of the testes consists of a mass of coiled tubules—the *seminiferous tubules*—bound to

ether by a *stroma* of connective tissue. The latter carries the blood vessels and forms septa which divide the body of the organ into a number of pyramidal lobes. The seminiferous tubules in their convoluted portions are lined by several layers of epithelial cells derived originally from the germinal epithelium; these give rise in the mature animal to spermatozoa. The epithelial lining of the tubules is homologous with the stratum granulosa of the Graafian follicle in the ovary. The different cell layers represent stages in the maturation of the male sex cells. The youngest cells—the *spermatogonia*—lie against the basement membrane; the more mature cells toward the lumen of the tubule. The spermatogonia give rise to *spermatocytes* (primary and secondary). The secondary spermatocytes divide to form *spermatids* which are transformed without division into mature *spermatozoa*. Proliferation of the spermatogenic cells is stimulated by the follicle-stimulating hormone of the anterior pituitary (p. 753). Other smaller columnar-shaped cells are found lying among the spermatogonia with their somewhat conical bases, resting upon the basement membrane. These are the *cells of Sertoli*. They take no direct part in the formation of the spermatozoa, serving merely to support and nourish the germ cells. In the stroma, isolated groups of polyhydral epithelial-like cells are present—the *interstitial cells* or *cells of Leydig*. These contain lipid granules in their cytoplasm, and are stimulated, apparently by the luteinizing hormone of the anterior pituitary.

THE PHYSIOLOGY OF THE TESTIS—THE MALE HORMONE

The testis has two functions, namely, the production of germ-cells—*spermatogenic function*—and the elaboration of male hormone—*endocrine function*.

The results of castration and transplantation experiments, an account of which has been given at the beginning of this chapter (p. 743) leaves no doubt that the testis is a gland of internal secretion. The earlier attempts to extract the testicular hormone were unsuccessful. The chief cause of failure was probably that a reliable test object had not been devised. Among the first to attempt the preparation of an active material was the noted physiologist Brown-Séquard (1889) who administered testicular extracts to himself and thought that he acquired an increase of vigor and a greater capacity for work after the treatment. The idea that senescence was related to testicular atrophy and the consequent reduction or loss of the male hormone was revived a few years ago by Voronoff in France and Steinach in Germany. Transplantations of apes' testes into old men have been performed and claims have been made that

the grafted tissue lives and causes rejuvenation of the recipient. The evidence, however, is far from convincing. There is no reason to suppose that testicular atrophy has any causal relationship to old age phenomena. Indeed, it is well known that in the male the degenerative changes of the body incident to age usually far outstrip the decline in the sexual functions. In the female, on the other hand, regressive changes in the ovaries occur normally after a certain age, yet this event does not appear to hasten senile changes. Nor do eunuchs show premature senility. Furthermore, the bodily changes associated with declining years are degenerative and irreversible; it is therefore irrational to hope that rejuvenation can be brought about by a hormone liberated from grafted testicular tissue. Moreover, any hormone effect which might result from such a procedure would be only temporary, for the graft does not live (p. 744).

The spermatogenic function of the testis is affected adversely by several conditions, namely, repeated or prolonged exposure to X rays or to radium emanations, alcoholism, vitamin E or B₁ deficiency, close confinement (in certain animals) and an elevation in temperature of the testis tissue amounting to only a few degrees. In the developmental anomaly known as cryptorchidism the testis fails to descend into the scrotum; spermatogenesis does not occur in the undescended organ. The defect is due undoubtedly to the relatively high temperature of the abdominal cavity which is several degrees above that of the scrotum. Raising the testis of the normal adult animal from the scrotum and fixing it in the abdomen is followed within a few days by degeneration of the seminiferous tubules. But the latter are restored to their normal appearance and function if the testis is returned to the scrotum, provided that its stay in the abdomen has not been too long. It has also been found that exposure for 15 minutes or so to a temperature of 6°C. above the normal body temperature leads within 10 days or so to degeneration of the sperm-producing cells. The latter effect follows in the ram if the scrotum is enclosed in heat-insulating material, such as coverings of wool, so as to maintain the scrotal temperature a few degrees above the normal level. Though the human testis may suffer in febrile diseases as a result of the high temperature the loss of function is, as a rule, only temporary.

The internal secreting function of the testis is resistant to the conditions mentioned above. The undescended testis continues to secrete its

hormone, for castration effects are not seen in bilateral cryptorchidism; nor does exposure to the X rays or vitamin deficiency lead to a failure in the endocrine function of the gonads.

Ligation of the vas deferens has been stated by some (e.g., Steinach) to cause degeneration of the spermatogenic cells and an increase in hormone production. These claims have been conclusively disproved. Vasoligation, which has been advocated as a means of increasing the output of male hormone, is based upon error and is never justified for this purpose; it exerts no detectable effect either upon the sperm-producing cells or upon those of internal secretion.

(1) Growth of the comb, wattles and ear-lobs of the castrated cockerel (capon) and of the cock in hens (fig. 309).

(2) Inhibition of ovulation in hens.

(3) Prevention of the atrophy of the accessory male organs (seminal vesicles, prostate, Cowper glands) in the castrated guinea pig, rat or mouse (fig. 310); the maintenance of the pendulous fold of the scrotum, and restoration of the electric ejaculatory response in the hypophysectomized guinea pig.¹⁴

(4) Extension of the lives (as judged by motility of the spermatozoa in the epididymis of hypophysectomized guinea pigs. This fact suggests



FIG. 309. Showing the effect of testis hormone (from urine) upon the comb growth of capons. The birds in the upper photograph received daily injections over a period of 15 days. Lower photograph, untreated controls. (After Funk, Harrow and Lejwa.)

In many wild species the activity of the male reproductive organs is confined to a definite mating season. The changes occurring during this period of "rut," as it is called, are analogous to those which take place during the estrus periods of the female. The testes hypertrophy, spermatogenesis occurs, and sexual desire is aroused. The anterior pituitary exerts a governing influence upon the testes essentially similar to that which it exerts upon the female gonads (p. 756).

Pezard as early as 1911 produced comb growth in capons by the injection of a saline extract of testicular tissue. McGee in 1927 obtained an active lipoid extract of bull's testes. As a result of the subsequent studies of this worker and his associates and those of other investigators (Moore, Gallagher, Koch) the following effects of testicular extracts have been demonstrated.

that the testicular hormone normally performs an important function with respect to the life and motility of the male sex cells. The spermatozoa when formed are non-motile, becoming so only upon reaching the epididymis where, apparently they are acted upon by the male hormone. Spermatogenesis in the immature (33 days old) rat can also be induced by injections of testosterone.

(5) Reduction in the size of the testes as a result of injury to the seminiferous tubules by repeated injections. This effect, as in the case of estrus upon the ovary (p. 748), is probably exerted through the hypophysis.

¹⁴ Passing an alternating electric current (30 volts) through the head of a normal anesthetized guinea-pig causes an ejaculatory reflex and the discharge of secretions from the vas deferens, seminal vesicles and prostate. This response was discovered by Batelli in 1922; it is abolished after castration.

(6) Restoration to normal of the "castration cells" of the anterior pituitary, (p. 756).

(7) Masculinization of female rat fetuses following repeated injections during pregnancy; hyperrophy of the uterus and reduction in the size of the ovaries of newly-born rats.

The testis hormone belongs to the class of sterols, being closely related chemically to the female sex hormones, to cholesterol, the bile salts, etc. (see p. 457). It has been obtained in crystal-

that of androsterone. The urinary androgens are apparently excreted as physiologically inactive glucuronides (see p. 749). Acid hydrolysis of the latter in the process of extraction liberates the active principles. *Androstenedione*, $C_{19}H_{26}O_2$, and *androstenediol*, $C_{19}H_{30}O_2$, are laboratory products, the former having been prepared from androsterone, the latter from dehydroandrosterone. Esterification of testosterone, as demonstrated by Parkes, greatly increases and prolongs its action,

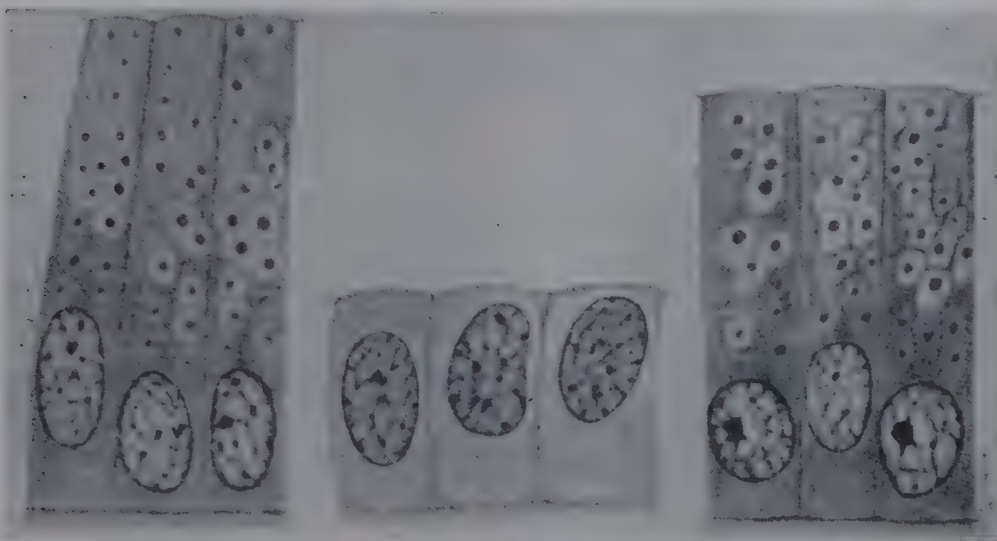
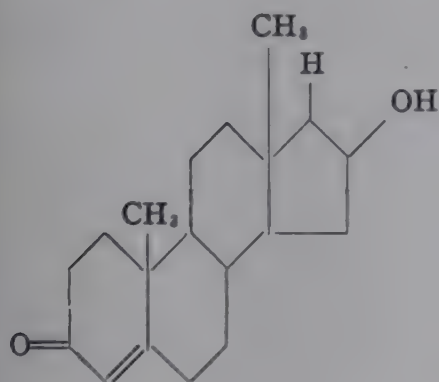


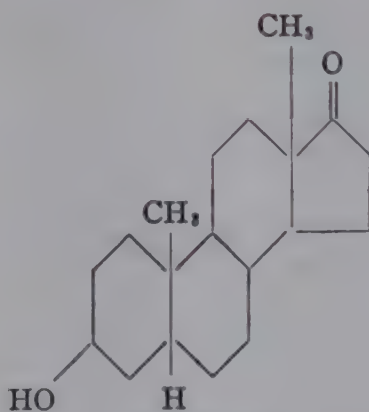
FIG. 310. Effect of castration and testis hormone on epithelium of seminal vesicles. (Moore, Hughes and Gallagher.) 1, cells from normal animal, showing secretion granules; 2, cells from twenty-day castrate; 3, cells from twenty-day castrate treated with male hormone.

ine form from testicular tissue; this product, which is regarded the true male hormone, has been named *testosterone*. Butenandt isolated a crystal-

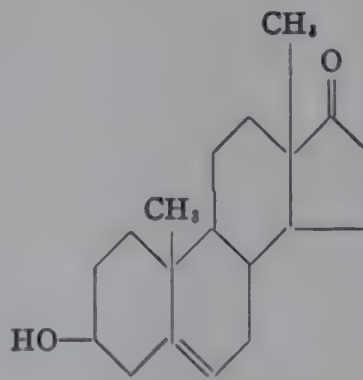
testosterone acetate and propionate, especially the latter, being several times more effective than the free hormone.



Testosterone



Androsterone



Dehydroandrosterone

line androgenic compound from urine. This is much less active (from $\frac{1}{4}$ to $\frac{1}{10}$) than testosterone and differs from the latter in chemical structure as shown in the formulae given below; it is called *androsterone*. Both testosterone and androsterone have been prepared from cholesterol by Ruzicka and his colleagues.

A second androgenic compound, *dehydroandrosterone*, is present in urine; its potency is about half

Testosterone is most effective when administered by injection; it is also effective percutaneously (by inunction) and by mouth but several times the injected dose is required. Androgenic substances (androgens) first make their appearance in male urine at the time of puberty or somewhat earlier. Androgens, surprisingly enough, are also present in female urine in amounts not greatly less ($\frac{1}{4}$) than in male urine and, as already mentioned, estrin

(probably estrone) is excreted by the male.¹⁵ The androgen/estrogen ratio (i.e., the number of international androgenic units excreted per day over the estrogenic activity in micrograms of excreted estrone per day) is from two to five times higher in males than in females (see Gallagher and colleagues). The main source of the androgens in female urine is the ovary, for ovaries grafted into the ears of castrated male rats maintain the seminal vesicles and prostate in a normal state (Hill); yet excretion is not entirely abolished by ovariectomy. It must be borne in mind that the male and female hormones are closely similar in chemical structure; estradiol can be converted to testosterone by dehydrogenation, and testosterone injected into a male is excreted partly as androgen and partly as estrogen. Furthermore, progesterone in large doses is capable of androgenic effects (the maintenance in castrates of spermatogenesis and enlargement of the prostate). The adrenal cortex probably furnishes a proportion of the androgens and estrogens found in normal urine, and all of those excreted after castration or ovariectomy. The excretion of both androgens and estrogens is reduced to around one-third of the normal in eunuchoidism and to small amounts after castration (human). In adrenal virilism (p. 698) the excretion of androgens may be, though not always, considerably increased.

Several methods have been proposed for assaying the potency of testicular preparations. Gallagher and Koch use the comb-growth test. They define a unit of testes hormone as the amount of extract which when injected daily for 5 days yields an average of 5 mm. increase in size (length plus height) of the combs of at least 50 per cent of a group of brown leghorn capons.

In animals which show a rutting season the male hormone is secreted intermittently, in others, e.g., the rat and guinea pig, and in man, the secretion is continuous. The elements of the testis which elaborate the hormone are not known with certainty, though it is generally believed that the interstitial cells of Leydig serve this function. The following is a summary of the evidence usually cited in support of this view.

(a) Treatment of the testes with mild doses of X-rays, or tying the vas deferens but leaving the spermatic vessels intact, results in atrophy of the

seminiferous epithelium; the interstitial cells remain unaffected and castration effects do not develop.

(b) When the testes are removed and grafted elsewhere in the body the seminiferous tubules degenerate but not the interstitial cells; castration effects are absent.

(c) When the testicles do not descend to the scrotum (cryptorchidism), the seminiferous tubules degenerate (probably as a result of the high abdominal temperature) while the interstitial cells are apparently unaffected. Subjects with undescended testes are sterile but are sexually normal otherwise.

This evidence for the belief that the cells of Leydig furnish the male hormone is not absolutely conclusive, for it cannot be stated with certainty that under any of the conditions mentioned the spermatogenic cells and the cells of Sertoli have not completely degenerated. Furthermore, in certain birds the cells of the seminiferous tubules show marked hyperplasia during the mating season, whereas the interstitial cells at this time become less prominent than they were previously.

Hypogonadism and hypergonadism in the male

Tumors of the testis in young boys may result in precocious development of the secondary sex characters—growth of hair upon the pubis, in the axillae and on the face, deepening of the voice and enlargement of the penis. These effects are evidently due to hypersecretion of the male hormone, they tend to subside after excision of the tumor. Hypergenitalism with closely similar features occurs as a result of hyperfunctioning of the adrenal cortex (p. 698). Failure of development of the accessory male sex organs and of the secondary sexual characters, a condition referred to as *hypogonadism* or *eunuchoidism*, is in most cases due primarily to a pituitary disorder. Deficiency of the gonadotropic hormone of the pituitary leads to atrophic changes in the testes, which may be greatly reduced in size, and to the suppression of their internal secretion. In other instances of eunuchoidism the testes are the primary site of disease, e.g., destructive new growths, mumps, typhoid fever, syphilis, etc. Testicular atrophy occasionally results from prolonged anorexia, severe inanition or of vitamin B₁ deficiency. Hypofunctioning of the testes may commence at any time during postpuberal life as a result of pituitary disease or of any of the conditions just mentioned. In the *deferred type of eunuchoidism* regressive changes, though usually of mild degree, in the accessory organs of sex and in the secondary sex characters may result. In many instances of hypogonadism in females as well as in males the excretion of gonadotropins in the urine is increased.

¹⁵ In some instances a part of the androgenic activity of urine, especially in cases of virilism (p. 698) may be due to the presence of *adrenosterone*, the androgen found in the adrenal cortex.

The sex hormones in relation to prostatic disease

The theory has been advanced that excessive production of male hormone is a factor in prostatic hypertrophy, it is an unquestionable fact that the male hormone (testosterone) stimulates prostatic growth. Nevertheless, it is improbable that hypersecretion by the interstitial cells is a factor in the causation of prostatic hypertrophy in man; secretion of the male hormone tends to decrease rather than to increase with advancing years.

It has been mentioned that estrin is excreted in the urine of the male and can be isolated from testicular tissue; it has also been shown by Zuckerman and Parkes that injections of estrin into monkeys causes prostatic hypertrophy, fibromuscular overgrowth of the whole prostate together with epithelial stratification and distension of the uterus masculinus. Such effects can be counteracted by injections of male hormone. These facts, taken in conjunction with the observation that the concentration of the male hormone in the urine of elderly men may be reduced while the excretion of estrin remains unchanged, have led some (de Jongh, Laqueur) to a conclusion as to the cause of prostatic hypertrophy in man which is opposed to that outlined above. They believe that an important factor leading to enlargement of the prostate is an imbalance between the male and female hormones—a *diminished* production of the former and, in consequence, a relative *excess* of the latter. In support of this hypothesis de Jongh states that injections of the male hormone in cases of prostatic enlargement prevents further hypertrophy and may actually cause shrinkage of the organ. Moreover, R. A. Moore and his associates observed that prostatic tissue of the rabbit transplanted into the anterior chamber of the eye showed a greater growth response to estrin than to male hormone administration. Nevertheless, observations opposed to this theory can be cited, e.g., the absence of excessive amounts of estrin in the blood or urine of subjects of prostatic hypertrophy, and the fact that estrin injections do not, apparently, aggravate the condition. The whole question of the causative factors in prostatic hypertrophy is rife with speculation and beset with contradictory observations and opinions. Established facts are few and difficult to obtain.

The epithelial cells of a prostatic adenocarcinoma are dependent for their growth and activity, as is the normal epithelium of the prostate, upon the male hormone. It is upon this basis that castration has been employed in the treatment

of prostatic cancer, the malignant growth, in many cases, undergoing regression after operation. Since androgen activity is antagonized or neutralized by estrogens, inhibition of the cancerous growth can also be induced by the administration of estrogenic material, e.g., stilbestrol.

The hormonal treatment of male sex disorders

The testis hormone, in accordance with the principle of hormone action in general (p. 670) does not stimulate the interstitial cells of the testes. Though highly successful results, of a temporary nature at least, have been reported following the use of the male hormone in underdevelopment or regression of the accessory sex organs, it is too early to attempt any real appraisal of its ultimate therapeutic value in these conditions.

The gonadotropic principle derived from pregnancy urine (p. 755) has been employed to stimulate spermatogenesis in an undeveloped testis or to restore the normal spermatogenic function which had been suppressed as a result of disease. Sterility in man is said to have been cured by this means; spermatozoa which before treatment were few and non-motile have, according to report, been increased in number and rendered actively motile after a series of injections of the anterior-pituitary-like hormone. Notable success has followed the use of the gonadotropic hormone of pregnancy urine in cryptorchidism, descent of the testes being induced. It has also been employed in various types of hypogonadism. The gonadotropic principle of the pituitary itself would be expected to give the best results but so far a reliable commercial preparation of this hormone has not been available.

THE THYMUS

Structure

The thymus arises from the third branchial cleft (and sometimes the fourth) on either side, each anlage going to form one of the lobes of the thymus. Each thymic lobe is composed of a number of lobules in which an outer portion or *cortex* and a central portion or *medulla* may be distinguished. The *cortex* resembles lymphoid tissue, being constituted of masses of small round cells—*thymocytes*—identical in appearance with small lymphocytes. The epithelial elements of the embryonic structure is almost entirely replaced during development by the ingrowth of these lymphoid cells from the surrounding mesenchyme. A small number of elongated reticular cells are seen scattered among the lymphoid elements. The *medulla* also contains lymphocytes but in fewer numbers; the reticular cells are thus

shown up more prominently and are seen to form a definite reticular stroma. Scattered throughout the medulla are round or oval elements from 30 to 100 microns in diameter known as *Hassal's corpuscles*. These bodies, which are the remnants of the original epithelial elements, are composed of cells arranged concentrically; they stain with acid dyes and therefore stand out conspicuously against the surrounding basophilic substance.

Possible Functions

The thymus of the infant is of relatively large size but during later childhood its weight in relation to body weight gradually decreases; little change in its absolute weight (25 to 40 grams) occurs; after the age of puberty a definite involutionary process commences. Though the involutionary changes, which consist of a reduction in the number of lymphocytes and reticular cells and their replacement by fat, are most marked during adolescence, they continue slowly throughout the rest of life. The corpuscles of Hassall disappear more slowly than the other elements.

It is admitted by most observers that the thymus serves a lymphopoietic function. Beyond this little is definitely known concerning its physiological rôle. It is enlarged in exophthalmic goiter, myasthenia gravis, adrenal insufficiency and in certain leukemic states. Thymic enlargement has also been considered to be a feature of the so-called *status thymico-lymphaticus*, a condition believed to consist of hypoplasia of the vascular system, a general increase in lymphoid tissue throughout the body, and a tendency to fatal syncope. Infants and young children who have died suddenly as a result of some trifling shock or during anesthesia have been thought to be subjects of this disease; it has been thought that enlargement of the thymus was in some way responsible. An investigation carried out recently by Turnbull and Young for the Medical Research Committee of Great Britain has failed to substantiate this belief. In the post-mortem examination of a number of children's bodies no relationship between the size of the thymus and vascular hypoplasia to the amount of lymphoid tissue in other parts of the body was found. In subjects dying suddenly as a result of shock or during anesthesia the thymus was not larger than in subjects dying from other causes. These investigators conclude that there is "no evidence that so-called *status thymico-lymphaticus* has any existence as a pathological entity." The possibility has been suggested that such cases of sudden death in infants are due to failure in function of the adrenal cortex.

The great body of experimental work which has been carried out in the past in efforts to elucidate the functions of the thymus have yielded little evidence which would enable it to be classified definitely among the glands of internal secretion. There is certainly no feature of its minute structure which suggests a glandular function. Numerous investigators, nevertheless, have claimed that their findings pointed to the thymus as playing an endocrine rôle. The problem has been studied both by the use of extracts of thymic tissue and by observing the effects of extirpation of the organ. Among the functions claimed for the thymus as a result of these two lines of investigation are, the regulation of calcium metabolism and the control of skeletal growth. Defective mineralization of the bones has been described

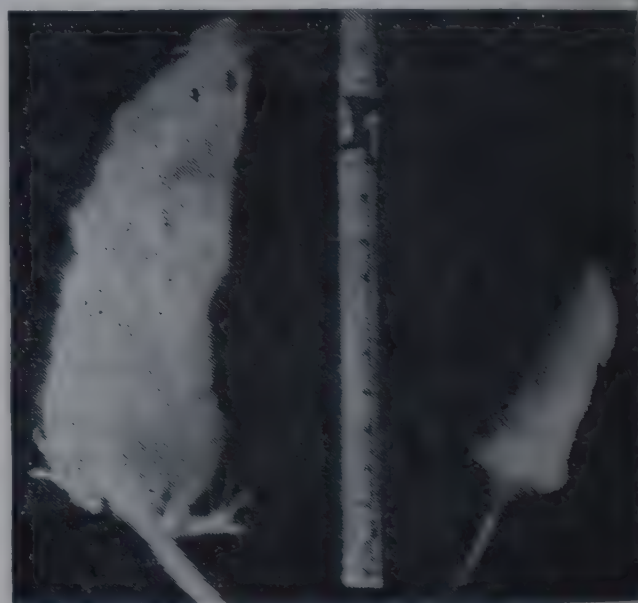


FIG. 311. At right, control rat 14 days old; at left, third generation thymus test rat 15 days old. (After Rowntree, Clark and Hanson.)

following thymectomy; others believe that the operation results in dwarfing. Gudernatsch found that feeding thymus tissue to tadpoles stimulated their growth but delayed metamorphosis. Thymectomy in pullets and pigeons is said to result in their laying eggs with uncalcified shells. Asch and his colleagues claim that thymic extracts contain a growth-promoting principle which they have named "thymocrescin," this material is said to stimulate the sex organs. The fact that thymic involution is delayed by castration but is most pronounced at the age of puberty has led several observers to the belief that the thymus is concerned in some way with sexual development.

Much of the earlier work on the thymus is very difficult to appraise, owing to the indecisive nature of the data or to the conflict between the results obtained by different workers in the field.

Anderson has made the interesting observation that rats exercised to the point of exhaustion show hypertrophy of the thymus and hypertrophy of the renal cortex. Selye has described similar changes following a variety of injurious agencies part of what he has termed the "alarm reaction."

Within more recent years Rowntree, Clarke and Anderson have reported spectacular effects following the intraperitoneal injection of thymus extract in successive generations of rats. Rats from the third to the seventh generation (F_3 to F_6) of a strain which had been treated in the preceding generations with thymus extract were described as showing an extraordinary acceleration of growth and development (fig. 311). The eyes and ears opened much earlier than usual and the body became covered with fur much sooner in the treated strain than in the controls. The treated animals increased rapidly in weight but, though the adult size was reached prematurely, they did not ultimately become larger than the controls. In males the testes descended at an unusually early age and fertility was increased. In the females showed pronounced sexual precocity, the vagina opening by the 20th day; litters were cast within from 40 to 45 days after birth. After the treatment had been continued for several generations its omission for one generation nullified the effects which otherwise would have appeared in the offspring of that generation. Thymectomy in several generations of parents resulted in retardation of growth and in the rate of development of the young. The effects upon the young of thymectomy of the parents were prevented by the treatment of the latter with extract. There has been no decisive confirmation of these results from other laboratories, and proof that the thymus possesses an endocrine function has not been obtained.

THE PINEAL BODY OR EPIPHYSIS

Origin and structure

This is a small gland-like structure (about 10 mm. long in man) somewhat resembling a pine-cone (pineal shape), situated just beneath the splenium of the corpus callosum and resting in the groove between the superior colliculi. The pineal arises as a diverticulum from the roof of the third ventricle. The cavity of the original pouch eventually disappears, the fully developed gland being composed of a solid mass of cells. The histological features of the pineal are very diverse, the picture varying from species to species and with age. In general however, it may be said to have a pseudo-lobular structure, the cells being arranged in masses or lobules surrounded by a highly vascular connective tissue. The cells composing these masses are of two main types. (a) *Parenchyma cells*. These are large cells with pale nuclei surrounded by a reticulated protoplasm

containing oxyphil granules. Each cell has numerous long processes, many of which end in club-like swellings. (b) *Neuroglial cells*. These are scattered among the parenchyma cells and, as a rule, are not numerous. Their long fibrous processes interlace with one another to form a framework for the lobule.

Involutionary changes are said to commence in the human pineal body about the seventh year. After this age laminated bodies composed of phosphates and carbonates of calcium and magnesium—the so-called "brain sand"—make their appearance.

Functions

The structure of the pineal has suggested an endocrine function but there is really little definite evidence from which such a conclusion may be drawn. In children destruction of this gland by disease has been followed in some cases by precocious sexual, skeletal and mental development, together with adiposity. However, in other instances of destructive disease of the gland no such developmental abnormalities have been observed. Dandy removed the pineal from puppies and found no sexual or somatic abnormality. The well-being of the animals was not affected. Horrax however, thought that the testes of guinea-pigs, rats and chickens showed precocious development after pinealectomy. He also reports a case of precocious sexual, mental and bodily development of a young boy in whom a pineal tumor was found at autopsy. Foa also reported hypertrophy of the comb and testes and the precocious development of sexual instincts in young male fowls after pinealectomy. These observations would suggest that the pineal normally exerts an inhibitory influence upon sexual development but Foa's results are far from being decisive. Recently Anderson and Wolf in a careful research found no effect of pinealectomy in young rats. The body growth, time of puberty or weights of the pituitary, thyroid, adrenal or thymus of either sex were not significantly influenced by the operation; no increase in the weight of the testes was noted and the estrus cycles occurred normally. McCord and Allen state that pineal feeding causes contraction of the melanophores of tadpoles.

It is clear from the equivocal or negative nature of the experimental results which have just been sketched that the function of the pineal, if indeed it possesses any physiological significance at all, is a riddle which so far has gone unanswered. The recent work of Rowntree and his colleagues suggests the possibility that the pineal like the thymus exerts an influence upon racial development. They report that pineal extract administered to parent rats in successive generations, results in retardation of growth but accelerated development of the young—"precocious dwarfism." Final judgment of this work must be reserved until the findings are confirmed.

SECTION VIII. THE NERVOUS SYSTEM

CHAPTER LXIII

INTRODUCTORY: THE PHYSIOLOGICAL PROPERTIES OF NERVE

THE STRUCTURE OF NERVOUS TISSUE

The structural unit of the nervous system is the *nerve cell* or *neuron*. Other elements—*neuroglial cells*—lying among the nerve cells serve as a supporting framework.

The neuroglia probably serves also as insulating material between neighboring neurons, preventing changes in electrical potential from spreading from one nerve fiber to another. The neuroglial cells possess numerous branching processes which interlace with one another to form a dense felt-work between the neurons (fig. 312). These interstitial cells of the central nervous system are present in both the gray and white matter; they vary greatly in size and shape and their processes in number and arrangement. Upon a basis of these differences they have been classified into three main types—*astrocytes*, *microglia* and *oligodendroglia*. The microglia are considered by most observers to be reticulo-endothelial elements (p. 78). They are migratory and phagocytic, wandering into the nervous tissue from the meninges along the blood vessels. In inflammatory processes involving the central nervous system these cells are increased in number. The oligodendroglia are believed to play a part in the formation of the myelin material which sheathes the nerve fibers. Though neurons do not multiply in the adult body and when destroyed are not replaced, certain neuroglial cells possess the power of active proliferation. This may occur to a marked degree in pathological processes.

Nerve cells show wide morphological variations in different parts of the nervous system. Even within relatively restricted areas the nervous elements may be of many different types. They may be small or large with pyramidal, rounded or irregularly shaped bodies. The number, structure, length and arrangement of their processes also show wide variations. Only those features common to the majority of nerve cell types can be described.

The neuron

The neuron consists of a *body* or *perikaryon* and two types of process—the *dendrite* and the *axon* (axis-cylinder process, fig. 313). The bodies of the nerve cells lie within the gray matter of the central nervous system or in outlying ganglia, e.g., posterior spinal root, cranial or sympathetic ganglia. The white matter of the brain and spinal cord and of the peripheral nerves is composed of bundles of nerve fibers. The core of each nerve fiber is formed by a process of a nerve cell. The gray matter receives a rich blood supply from the vessels

of the pia mater; the blood supply to the white substance is much less profuse.

By means of special staining methods three structures can be distinguished in the cytoplasm of the cell body (a) *neurofibrils*, (b) *Nissl bodies* or *tigroid substance* and (c) *the internal reticular apparatus of Golgi*. The neurofibrils are very fine filaments which stream through the cytoplasm from dendrite to axon (fig. 314); they enter the latter process and extend to its terminations. The Nissl bodies are granular masses stainable with basic dyes. They give a striped or tigroid appearance to the cell (fig. 315A). They are absent from the region of origin of the axon and vary in size and number in accordance with the functional state of the neuron; they undergo disintegration (chromatolysis) in a fatigued or injured cell or in one whose axon has been sectioned (p. 779). The internal reticular apparatus of Golgi is a coarse network seen within the cells when special methods—e.g., impregnation with silver chromate—are employed which leave the Nissl bodies and the neurofibrils invisible (fig. 315B). The surfaces of most perikarya are covered by a fine network—the *superficial reticulum of Golgi*. The nucleus of the nerve cell contains a well defined nucleolus, but as a rule no centrosome.

Though the nerve cell frequently possesses more than one dendrite the axon is single. The dendrites may divide into numerous branches a short distance from their origin from the cell body to form a tree-like structure (in the central nervous system) or they may run for long distances (several feet, as in the peripheral sensory nerves) before they break into their terminal branches. The axon arises from a small elevation on the surface of the cell body—the *axon hillock*. It may give off short collateral branches or may run as an unbranched fiber, not dividing until it has reached its destination. The dendrite is the receptive process of the neuron, the axon the discharging process, i.e., the former transmits the impulse towards, the latter away from the cell body. Nerve fibers which carry impulses to the central nervous system are termed *afferent*; those conveying impulses from the central nervous system to the periphery are called *efferent*. Purely sensory (afferent) nerves are therefore composed, strictly speaking, of dendrites, and purely motor (efferent) nerves of axons. A mixed nerve contains fibers of both types.

Structure of the nerve fiber

The axons and dendrites so long as they remain within the gray matter are simple protoplasmic exten-

sions of the cell body, but upon entering the white matter they become invested by a layer or lipoid material called *myelin*. This covering is known as the *myelin sheath*. In the peripheral nerves, but not in the central nervous system, the myelin sheath is enclosed in turn by a nucleated membrane, the *neurilemma* or *sheath of Schwann* (fig. 313). In peripheral nerve fibers the myelin sheath is interrupted at regular intervals. The neurilemma dips into the gaps so formed to give the appearance of evenly spaced constrictions known as the *nodes of Ranvier*. Toward its termination the nerve fiber loses its myelin covering, being then clothed simply by the neurilemma. The latter is finally lost, the fiber terminating as a naked axis cylinder. The processes arising from sympathetic nerve cells (post-ganglionic fibers) are devoid of a myelin covering. They are invested simply by a sheath of Schwann and are therefore called *amyelinated* or *nonmedullated* fibers.



FIG. 312. Neuroglia cells. Upper, astrocyte; lower, oligodendroglia cell.

Myelination of fiber tracts in the central nervous system

The nerve fibers in the various conducting pathways receive their myelin sheaths at different ages and it is generally believed that the myelination of a given tract and the time at which it commences to function coincide. The sensory tracts become myelinated first, those of the posterior columns of the spinal cord between the fourth and fifth months of fetal life (human). The spinocerebellar tracts are myelinated later and the motor paths, e.g., corticospinal (pyramidal) tracts do not commence to receive their myelin sheaths until the second month of life and are not completely myelinated until about the second year, or about the time when the child has learned to walk. The fibers of association paths, for the most part, myelinate at still later dates.

Neurobiotaxis

Kappers explains the development of conducting pathways in the central nervous system upon the theory

that the body and dendrites of a nerve cell move, as a result of some attractive force, toward the point from where its stimuli come. Its axon lengthens in the opposite direction. Kappers terms this process *neurobiotaxis*. The nature of the attractive force is unknown, though it has been suggested that neurobiotaxis is a galvanotropic effect, the point in the nervous tissue in receipt of stimuli being electrically negative, presumably, to its surroundings. The theory

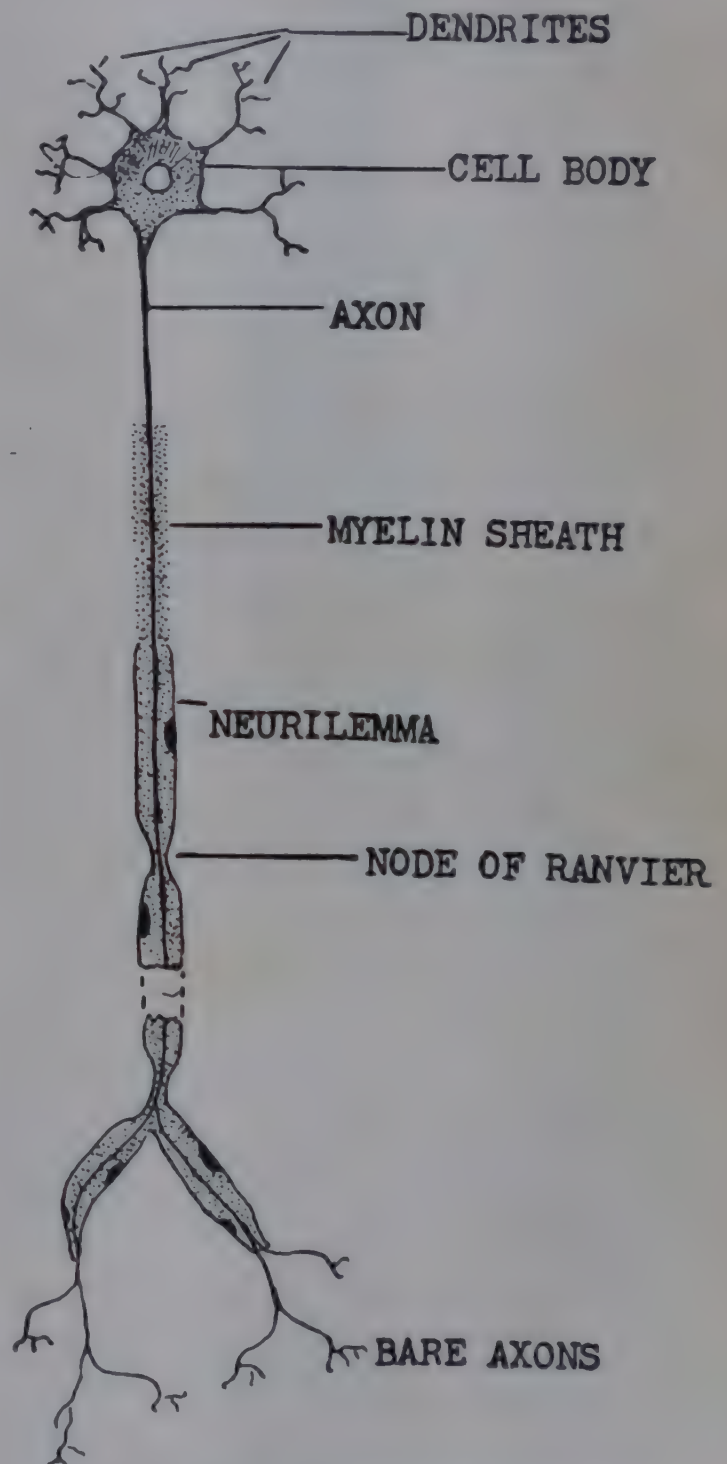


FIG. 313. Showing different parts of the neuron.

of neurobiotaxis offers a ready explanation for the development, as a result of experience and training, of the innumerable reflex arcs within the central nervous system and of the multiplication of association pathways. The close relation of the eye muscle nuclei to the medial longitudinal bundle, through which impulses from numerous sources are received, and the peculiar course of the fibers of the facial nerve within

the pons, are other examples which are believed to illustrate the operation of this principle. The course taken by the facial fibers, which arch over the abducens nucleus, is attributed to the migration of the facial nucleus toward the tractus solitarius and the sensory nucleus of the trigeminal, from both of which the facial neurons receive impulses.

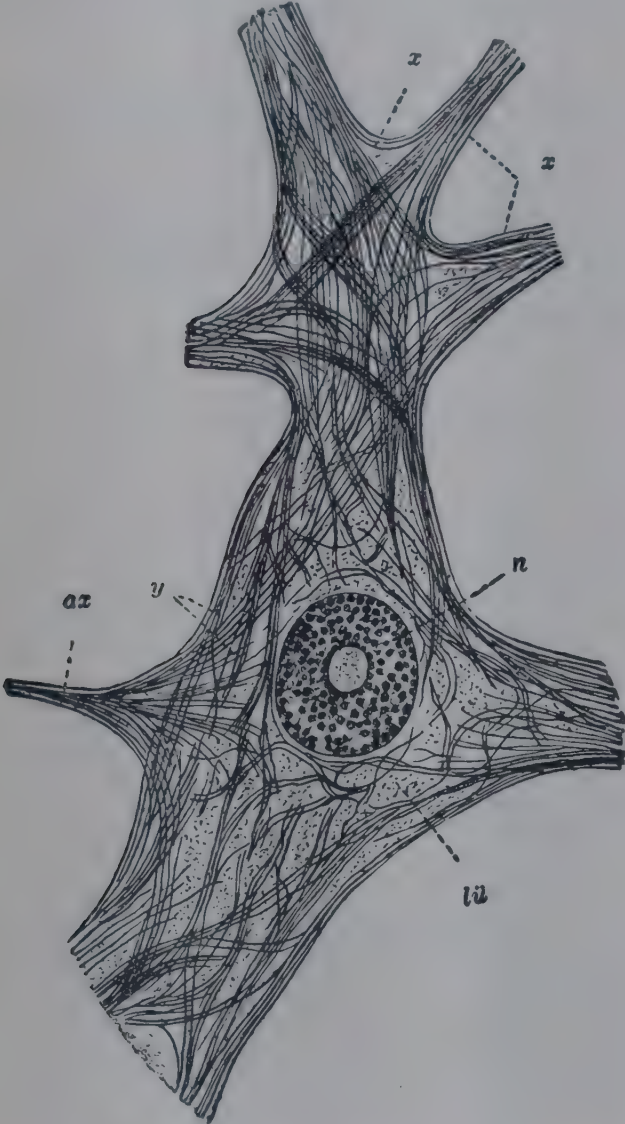


FIG. 314. Showing neurofibrils in a cell from the anterior gray column of the human spinal cord. *ax*, axon, *lu*, interfibrillar spaces; *n*, nucleus; *x*, neurofibrils passing from one dendrite to another; *y*, neurofibrils passing through the body of the cell (from Ranson, after Bethe and Heidenhain).

NERVE DEGENERATION AND REGENERATION

When a nerve fiber is divided the portion peripheral to the point of section, being separated from the body of the cell, undergoes degenerative changes. It is generally believed that the degenerative process does not start first at the point of section and progress to the periphery, but that it involves all parts of the fiber simultaneously, even to the finest terminals. The first change is noted in the neurofibrils which become tortuous and show irregular thickenings. The myelin sheath next becomes swollen and breaks up into small ovoid segments (fig. 316). Later, decom-

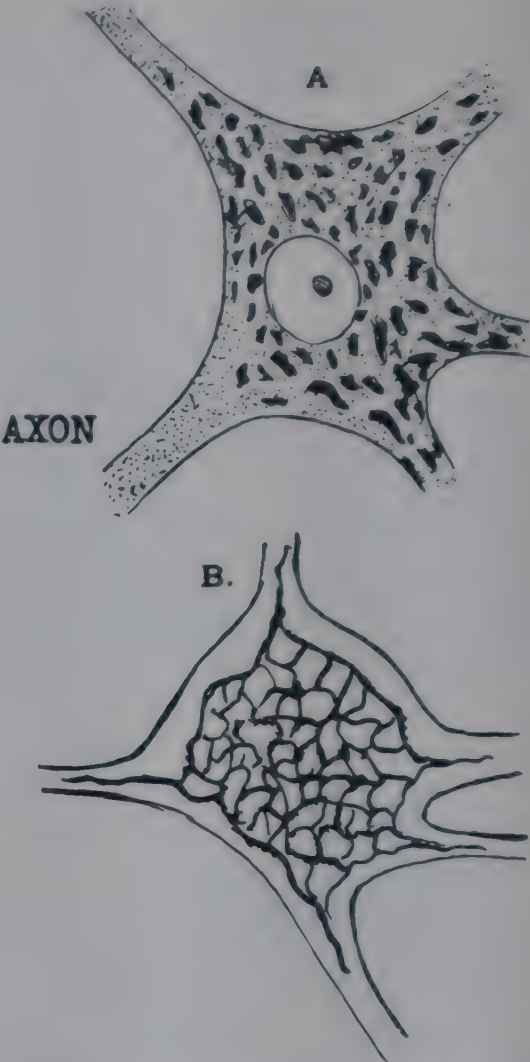


FIG. 315. A, showing Nissl bodies; B, internal apparatus of Golgi.

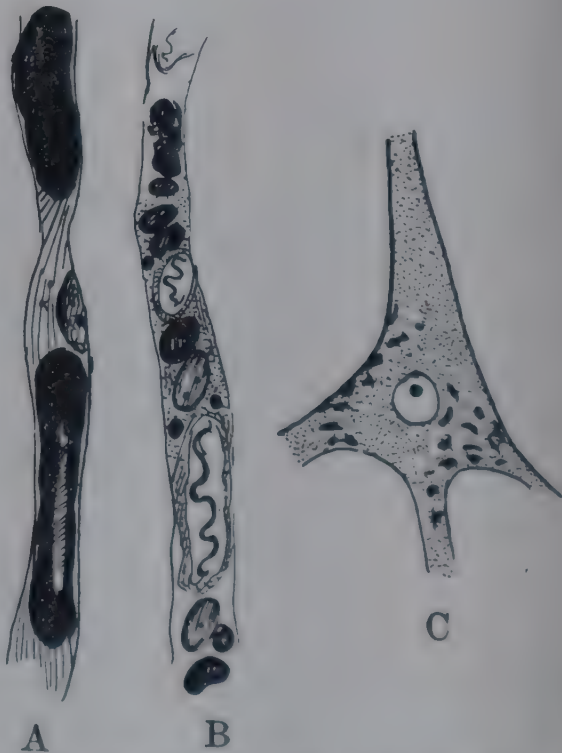


FIG. 316. Degenerating nerve stained with osmic acid. A, shows appearance of distal segment of nerve fiber 2 days after section, note large masses of myelin derived from medullary sheath; B, 5 days after section, smaller myelin particles together with droplets of fatty acids and fragmented neurofibrils; C, retrograde degeneration in cell body, disintegration of Nissl bodies.

position of the myelin occurs; droplets of kephalin and lecithin appear; derivatives of the latter—choline, glycerophosphoric acid and unsaturated fatty acids—can be detected. The fatty acids are responsible for the brown staining of the degenerated nerve when treated with osmic acid. The nuclei of the neurilemma proliferate, and the cytoplasm becomes swollen and vacuolated. The neurofibrils undergo fragmentation; they and the protoplasm surrounding them finally undergo complete disintegration, the debris intermingling with the material of the disorganized myelin sheath. Subsequently the degenerated materials disappear, and all that remains of the nerve fiber is the empty neurilemma tube. The foregoing changes were first described by Waller and are spoken of as *Wallerian degeneration*. Alterations (which were not recognized by Waller also occur in the neuron on the proximal side of the section (*retrograde degeneration*). The nerve fiber as far centrally as the first node of Ranvier shows changes similar in nature to those just described. In the perikaryon itself, swelling of the cytoplasm and nucleus occurs and the Nissl granules undergo disintegration (*chromatolysis*). Atrophy of the cell body may ultimately result.

Regeneration. This occurs in peripheral nerve fibers, but not in those of the central nervous system, the presence of a neurilemma being essential for the process. Section of the sensory root of the trigeminal nerve, for example, for the relief of severe neuralgia of the face, is not followed by regeneration of the fibers within the brain. Nor does regeneration of the optic nerve, whose fibers do not possess neurilemma sheaths, occur.

Regeneration is accomplished by a downgrowth of the neurofibrils from the proximal segment of the cut nerve. These enter the empty neurilemma sheath of the distal segment and in time traverse its entire length. The rate of growth in man has been variously estimated (from 1.0 to 4.5 mm. per day); it is influenced by many conditions. The cells of the neurilemma form a protoplasmic matrix for the sprouting neurofibrils. The neurilemma of the lower segment grows upwards and if the gap is not too long joins the neurilemma of the upper segment which has formed around the developing axis cylinder. The myelin sheath is developed some time later. The young axis cylinders may traverse the tissues for relatively long distances in order to enter the neurilemma of the lower segment. The force responsible for this remarkable phenomenon (neurotropism) is unknown. The attraction may be due to the liberation of

chemical substances by the proliferating neurilemma cells of the lower segment. If the gap separating the two segments is wide and occupied by scar tissue, an effectual block may be offered to the regenerating fibers; these nevertheless continue to grow in a tangled, curled fashion and may produce a localized mass of tissue composed of nerve fibers embedded in connective tissue (*neuroma*). In those cases of nerve injury in which, as a result of pressure or crushing, the axis cylinder is interrupted without division of the neurilemma, the conditions for regeneration are most favorable.

The remarkable rapidity of regeneration of preganglionic sympathetic fibers has been demonstrated by Haimovici and Hodes. In a three-stage operation upon cats large section of the sympathetic chains below their cervical portions were excised. Stimulation of the cephalic end of a cervical sympathetic stump as early as 54 days after the last stage of the operation caused pupillary dilatation and retraction of the nictitating membrane.

The regenerating fibers of one nerve will grow into the sheath of the lower segment of another, though less readily than into its own sheath, and even the fibrils of a sensory nerve will grow into the distal segment of a motor nerve or vice versa. The central stump of one nerve will not, however, grow into the central stump of another. The proximal end of the hypoglossal or spinal accessory, for example, has on many occasions been anastomosed to the distal end of a paralyzed facial nerve with a successful functional result. Cannon, Binger and Fitz united the phrenic in cats to the cervical sympathetic low in the neck and later observed a rise in metabolism, nervous excitability and increased heart action which were attributed to stimulation of the thyroid by impulses discharged from the respiratory center. This experiment was repeated by Horrax, and more recently by Friedgood and Cannon, with essentially the same result. The effect is probably not a direct one upon the thyroid but is due to stimulation of the pituitary and the release of its thyrotropic hormone. Balance and Duel, also experimenting with cats, anastomosed the central end of the hypoglossal to the peripheral cut end of the cervical sympathetic, and reported that the normal pupillary reactions were restored. Restoration of function does not follow the union of a motor with a sensory nerve, nor of a cholinergic with an adrenergic nerve (p. 950).

It has been shown by Tello in animals and by

Duel in man that when a nerve has been severed a much better functional result is obtained if from 2 to 3 weeks are allowed to elapse before the divided nerve is sutured. The reason for this is that the degenerated material in the distal segment has had time to be cleared away; thus, an unobstructed neurilemma tube is left for the downward growth of the neurofibrils of the upper segment. Otherwise, apparently, some of the neurofibrils upon meeting the degenerated debris are diverted from their course.

Degeneration of the facial nerve in the facial canal as a result of middle ear disease (Bell's palsy, p. 860), trauma, etc., has been treated with outstanding success by Duel. The affected portion of the nerve is excised and a graft, constituted of a section of the anterior femoral cutaneous nerve, is used to fill the gap. For the reason just given the latter nerve is sectioned and left in place for 2 or 3 weeks before it is employed in the grafting operation.

Electrical reactions of nerve and muscle. Reaction of degeneration

A motor nerve may be stimulated through the skin by either the faradic (interrupted) or the galvanic (constant) current. The muscle contracts so long as the faradic current flows but only during the make (closure) or break (opening) of the galvanic current; for a given strength of current closure shocks are more effective than opening shocks. In testing the reactions one electrode is placed upon the skin of some indifferent part of the body (*indifferent electrode*) and another smaller electrode (*stimulating electrode*) is placed upon the skin overlying the nerve trunk or muscle which it is desired to stimulate. In the latter instance the nerve terminals within the muscle are stimulated, not the muscle fibers themselves. The stimulating electrode is applied over that part of the muscle which gives a response with the least strength of current; this is spoken of as the *motor point* and corresponds to the point of entrance into the muscle of the motor nerve. When the stimulating electrode is attached to the positive pole of the battery it is called the *anode*. The current enters the muscle by this electrode and leaves the body by the indifferent electrode which is then called the *cathode*. When the galvanic current is reversed, the stimulating electrode becomes the cathode and the indifferent electrode the anode. Normally the least strength of current is required when the cathode overlies the muscle and the circuit is closed. The response which follows such a shock is called the *cathodal closing contraction* (abbreviated C.C.C.). The next most easily elicited response is the *anodal closing contraction* (A.C.C.), i.e., when the stimulating electrode is the anode and the current is closed. The *anodal opening contraction* (A.O.C.) is less easily evoked than the last, and the *cathodal opening contraction* (C.O.C.)

requires the strongest current of all. The four actions in the order of the strength of current required for their elicitation may be expressed thus:

$$C.C.C. < A.C.C. < A.O.C. < C.O.C.$$

The normal relationship between current strength and these responses is also shown in the following table.

STRENGTH OF CURRENT	REACTION
Weak	C.C.C.
Medium	C.C.C. and A.C.C.
Strong	C.C.C., A.C.C., A.O.C.
Very strong	C.C. tetanus, A.C.C., A.O.C. and C.O.C.

The investigation of these reactions is of considerable value in the detection of degeneration of a motor nerve and in the diagnosis of a lower from an upper neuro lesion (p. 865). Lengthening of the chronaxie of nerve occurs during the earlier stages of its degeneration; it therefore fails to respond to the brief shocks of faradic stimulation but a sluggish contraction of the muscle follows stimulation with the galvanic current. Later the nerve becomes quite incapable of being excited by either the faradic or the galvanic current. When the nerve terminals have degenerated the chronaxie of the muscle is lengthened and the faradic current applied directly to the muscle causes no response; the muscle responds, however, though in an abnormal manner, to the galvanic current, the fibers being *directly* stimulated. The response of the muscle shows the following features. (a) Sluggishness of contraction and relaxation. (b) The response is elicited with a weaker current than normally, i.e., the muscle is hyperexcitable to the galvanic current. (c) The anodal closing contraction (A.C.C.) may often be elicited more readily, i.e., with a weaker current, than the cathodal closing contraction (C.C.C.). Thus, $A.C.C. < C.C.C.$

These changes in the electrical responses of nerve and muscle, namely, loss of excitability of nerve to faradic and galvanic stimulation, failure of the muscle to respond to faradic stimulation and the abnormalities of the reaction to galvanic stimulation just described constitute the *complete reaction of degeneration* (C.R.D.). When the nerve is still capable of being excited by galvanic but not by faradic stimulation but the muscle responds weakly or not at all to the faradic current, the reaction of degeneration is said to be incomplete—*partial reaction of degeneration* (P.R.D.).

THE PHYSIOLOGICAL PROPERTIES OF THE NERVE FIBER

EXCITABILITY AND CONDUCTIVITY

The nerve fiber may be stimulated electrically, thermally, chemically or mechanically. Any one

of these types of stimulus causes a change in the nerve at the point of stimulation which may be termed the *local excitatory state*. If this attains a certain value a wave of excitation is transmitted along the nerve fiber. The propagated disturbance is referred to as the *nerve impulse*, and its passage from point to point along the fiber as *conduction*.

THE CHARACTERS OF A STIMULUS

A stimulus may be defined as any change in the environment of a tissue which causes it to react. In experimental work the electric current is usually employed as the stimulus on account of its convenience and the accuracy with which it can be measured. It also leaves the tissue undamaged. In order to induce a local excitatory state in a nerve of sufficient value to set up an impulse, a stimulus must answer the following requirements.

(a) *Intensity or strength*

When electrical stimulation is employed the intensity corresponds, practically, to the voltage. It is well-known that while a strong stimulus will cause a response, a weaker one may fail to do so. The stimulus which possesses just sufficient strength, and no more, to set up an impulse is said to have an intensity of *threshold* (*liminal*) value. Stimuli of less strength than this are called *subthreshold* (*subliminal*) or *subminimal*. A subthreshold stimulus does not, however, leave the nerve unaffected for, if a second stimulus also of subthreshold strength, or a series of such stimuli, be sent into the nerve an impulse is set up. The first stimulus is believed to cause a local excitatory state, or "local potential" (Hill), which, though of too low a value to set up an impulse, can be built up to the requisite level by a second, or a series of subthreshold stimuli, applied at short intervals. The phenomenon is spoken of as the *summation of inadequate stimuli*.

(b) *Duration*

When a constant current is passed through nerve or muscle, excitation occurs only when the circuit is completed. For this reason the duration of the current flow was believed in the past to bear no relationship to its ability to excite. The strength of the current and the rate at which this developed to a maximum ((a) and (b) above) were considered to be the sole factors determining the effectiveness of the stimulus. Though it is true that no physiological effect is produced in the nerve by prolonging the period of current flow indefinitely,

nevertheless the current must flow for a certain period in order to be effective. For example, high frequency alternating currents of very high voltage (tesla) may be passed through the body with impunity.¹ Presumably then, a certain period of time is required for the current to bring about those changes in the nerve upon which the excitatory state depends. The brief effective period following the commencement of the current flow is called the *serviceable* or *utilization time* (*temps utile*). It is measured in thousandths of a second. When, for instance, a current of a certain voltage and having a duration of say 3 sigmas (σ)² just fails to excite the tissue, then either increasing the voltage or prolonging the duration of the current causes a response. Or, if a current of a certain voltage and duration is just capable of exciting the tissue, reducing either of these factors renders the stimulus ineffective. The length of the utilization time varies in different tissues, but for the frog's gastrocnemius it is about 3.0 sigmas. Beyond the utilization period no relationship exists between the intensity and the duration of the current. Therefore when the current is of indefinite duration its effectiveness depends entirely upon its intensity. The intensity (voltage) of a current which when allowed to flow for an indefinitely long period is just capable of exciting the tissue (intensity threshold) is called the *rheobase*. The relationship between strength and duration of current is shown in figure 317.

CHRONAXIE. It is evident from the foregoing paragraphs that the excitability of a tissue may be determined in one or other of two ways: (a) by ascertaining the minimal strength of a current which when allowed to flow for an unlimited period will excite (intensity threshold), or (b) by measuring the minimal time during which a current of a standard strength must flow in order to excite (duration threshold). Lapicque employs the latter or, as he has termed it, the *time characteristic* or *chronaxie*, considering it a more accurate measure of excitability. A current having a strength twice the rheobase is employed, and the minimal duration of flow necessary for excitation is measured. *The chronaxie may therefore be briefly defined as the shortest duration of a current necessary for excitation when its strength is twice the rheobase.*

¹ Heating of the tissues traversed by the current occurs however.

² A sigma or milisecond (m.sec.) = $\frac{1}{1000}$ second.

Determinations of chronaxie may be carried out by the use of (a) a *constant current* which by means of a special type of rheotome is allowed to flow through the tissue for a very brief accurately measured period, (b) *condenser discharges*. The duration of a condenser discharge is proportional to the capacity (C) of the condenser, provided the resistance (R) in the discharge circuit remains constant. By charging condensers of different capacities (measured in farads) to different potentials, currents of any desired duration or voltage can be employed. In order to render any variation in the resistance of different tissues negligible a high resistance (15,000 to 20,000 ohms) is introduced into the discharge circuit. In determining the chronaxie by means of condenser discharges the current of minimal voltage required for excitation is first determined, a very high capacity, i.e., one with a long discharge, being used. The threshold voltage (rheobase) is then doubled and the lowest capacity is found

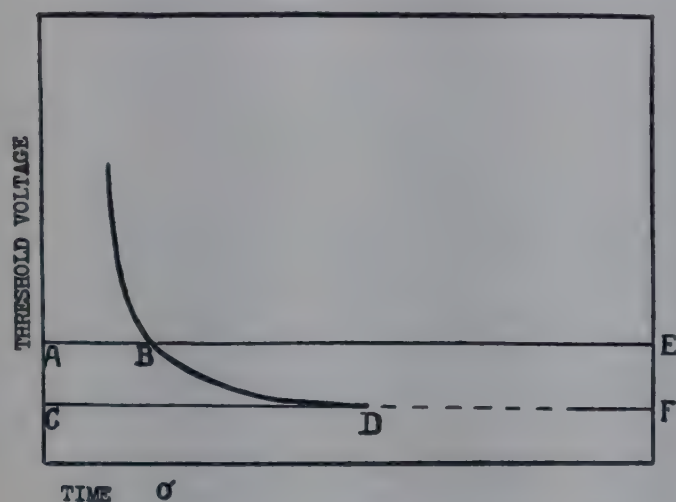


FIG. 317. Strength-duration curve. The line A B E represents a strength of current twice the rheobase (C D F). The distance A-B therefore represents the chronaxie, i.e., the required duration for excitation of a current having a strength twice the rheobase. The distance C-D indicates the utilization time.

(shortest duration of discharge) which will produce a response at the higher voltage. The result is obtained in microfarads. Since the time, or chronaxie, is proportional to the product of the capacity and the resistance in the discharge circuit, the result can be converted into seconds by the following formula:

$$\text{Chronaxie} = C \text{ (farads)} \times R \text{ (ohms)} \times K.$$

$$(K = 0.37)$$

Rapidly reacting tissues have a shorter chronaxie than the more slowly acting. The chronaxies of smooth muscle and its nerves are longer than those of skeletal muscle and somatic nerves. The tissues of cold-blooded animals have, in general, longer chronaxies than the tissues of higher forms. Flexor muscles have shorter chronaxies than extensors and the chronaxies of the more rapidly acting white muscles are shorter

than those of the red. Nerve fibers of large diameter and of more rapid conduction respond to shorter durations of current than do the thin and slower fibers. The chronaxies of sensory nerves are in general about the same as those of the corresponding motor nerves. The chronaxie of the ventricular muscle, contrary to expectation, is shortened by vagus stimulation, or by drugs such as acetylcholine which slow the cardiac rate and lengthened by accelerator stimulation or by drugs, e.g., atropine and adrenaline, which cause acceleration. The chronaxie of the junctional tissues is about three times longer than that of auricular or ventricular muscle. The chronaxie of the gastric muscle is also shortened by vagus stimulation. The chronaxie is lengthened by cold and shortened by a rise in temperature. Stretching cardiac or smooth muscle reduces the chronaxie; and that of skeletal muscle is lengthened by fatigue and shortened by adrenaline. The utilization time (temps utile) of a tissue varies with its chronaxie, being about 10 times the value of the latter. Thus the chronaxie of the frog's gastrocnemius is 0.3σ , the effective period is 3.0σ .

In table 73 are compared the values for chronaxies and utilization periods for different tissues.

The theory of isochronism. Lapique maintains that normally the chronaxie of a muscle and that of its nerve are of the same order—the value of one not being greater than that of the other by more than 100 per cent. He claims that this so-called *isochronism* is essential for the transmission of the impulse from nerve to muscle. A chronaxie difference greater than 100 per cent between a muscle and its nerve or between any other two successive parts of the conducting pathway (i.e. between neurons), is termed *heterochronism*. It acts as a block to the passage of the impulse. Certain muscular poisons act, it is supposed, by inducing heterochronism. Curare, for example, which does not paralyze either the muscle or its nerve was previously supposed to act upon a special “receptive substance” situated between the nerve ending and the muscle fiber. According to Lapique, the drug acts by lengthening the chronaxie of the muscle but leaving that of the nerve unaffected, i.e., heterochronism is induced. In support of the theory, it is pointed out that when a nerve-muscle preparation is treated with either veratrin or strychnine the muscle can no longer be stimulated through its nerve. Veratrin shortens the chronaxie of the muscle, strychnine that of the nerve. In either case heterochronism is induced. When, on the other hand, the preparation is treated with the two drugs simultaneously the impulse is not blocked since, the chronaxies of both nerve and muscle being shortened, isochronism is maintained. The onset of muscular

fatigue is attributed to the development of heterochronism between the muscle and its motor nerve.

The theory of isochronism has been criticised by Rushton, to whose article the reader is referred; this observer was unable to confirm Lapicque's finding regarding the actions of curare, veratrine and strychnine. At the best the theory appears to be only an approximation and strict isochronism is not a necessary condition for neuromuscular transmission.

Chronaxies in the human subject have been investigated under various physiological conditions and in many pathological states by Bourguignon and others. Condenser discharges are employed, an indifferent electrode being placed upon the skin over the sternum and the stimulating electrode, as the cathode (p. 780), upon the skin overlying the nerve or muscle to be

of a stimulus increases gradually to its maximum value, this must be much greater in order to evoke a response than when the rise in intensity is more rapid. The type of electrical stimulus usually employed rises to its maximum value within $\frac{1}{1000}$ second; however, if the strength of a current, which at this rate of change was just capable of evoking a response, rises more slowly to its peak excitation does not occur.

In seeking an explanation of this fact it might reasonably be assumed that the changes (e.g., ionic redistribution) in the nerve fiber associated with the local excitatory state or "local potential" (V) built up as a result of the stimulus, are opposed by processes of a

TABLE 73

SPECIES	TISSUE	CHRONAXIE	TEMPS UTILE	DURATION OF CONTRACTION
		σ	σ	seconds
Dog	Ventricular muscle	2.0	—	0.16
	Ventricular muscle during vagal stimulation	0.8	—	—
	Bundle of His	6.0	—	—
Frog	Gastrocnemius	0.3	3.0	0.1
	Stomach	100	—	15-20
	Sciatic nerve (conduction 30 m. per second)	0.3	3.0	—
Turtle	Ventricular muscle	9.0	80	—
	Leg muscles	1-2	—	1.0
Crab	Claw muscle	12	300	0.5
Leech	Nervous chain (conduction 0.4 m. per second)	30	—	—
Man	Flexors of thigh	0.10-0.16	—	—
	Extensors of thigh	0.44-0.72	—	—
	Flexors of arm	0.08-0.16	—	—
	Extensors of arm	0.16-0.32	—	—
	Retina	1.2-1.8	—	—
	Vestibular N	14-22	—	—
	Taste buds (tip of tongue)	1.6	—	—

investigated. The chronaxies in the new-born child are about 10 times longer than those of the adult. The longer chronaxies are in agreement with the much slower movements of the infant. Heterochronism exists between the muscles and their nerves until about the 15th month (walking age). The lengthening of the chronaxie of a degenerated nerve and its muscle has already been mentioned (p. 780). In diseases of the central nervous system all muscles which are the seat of paralysis show lengthened chronaxies and in progressive nervous disease those groups of muscles of similar chronaxies are usually attacked more or less simultaneously.

(c) *The rate of change in the intensity of the stimulus —accommodation in nerve*

Rapid change in environmental conditions is an essential factor in excitation. When the intensity

reverse kind tending to restore the nerve to its resting condition. If the stimulus increases in intensity at a sufficiently rapid rate the building up processes outstrip those of a restorative nature until the local potential reaches a critical value, when excitation (impulse production) occurs. When the current ceases to flow V returns gradually, and it is assumed exponentially, to its original value (V_0). According to Hill, the simplest possible expression for the return of V to V_0 is:

$$\frac{dV}{dt} = (V - V_0)K.$$

Where K is the *time-constant of excitation*. The chronaxie then is $K \times 0.693$. In theory it is more precise, in defining K , to deal with the decay of V to V_0 than with the rise of V_0 to V , as the former is then not affected by the nature of the stimulus used.

A second time factor in excitation called the "*time-constant of accommodation* (λ)" has been studied by Hill and Solandt. It is a measure of the rate of change in the critical value of V , which may be designated as the threshold U , under the influence of the stimulus. If the stimulus rapidly reaches the strength required for excitation, U is constant and independent of the previous history of the nerve, but if the stimulus intensity increases more gradually the threshold rises from its resting value (U_0) to some higher value (U). λ is determined by measuring the rate at which U returns to its initial level (U_0). The relationship may be formulated thus;

$$\frac{dV}{dt} = \frac{(U - U_0)}{\lambda}$$

Thus, whereas K is the time-constant of the rate of decay of the excitatory state or local potential, λ is the rate at which, after accommodation, the threshold returns to its original value. The value of λ (35 sigmas for sciatic nerve of the frog and 58 for human ulnar nerve) is normally from 10 to 20 times that of K . However, K and λ vary independently of one another.

The time factor of accommodation is altered by several conditions, the most notable being changes in calcium ion concentration. An increase in concentration of ionic calcium reduces the value of λ , that is, the neuromuscular tissues accommodate more readily, which means that more rapid changes in stimulus strength are required for excitation. Reduction in ionized Ca, as in tetanic states, exerts the reverse effect—increased value of λ , and reduced accommodation of the neuromuscular tissues which are in consequence excited by relatively slow rates of change in the strength of the stimulating current (see p. 702). If the calcium ion concentration is sufficiently low there may be a complete absence of the phenomenon of "accommodation."

THE NERVE IMPULSE

The nerve impulse is a self-propagated disturbance. That is to say, the energy for the transmission of the impulse is derived from the nerve fiber over which it passes. Nervous conduction therefore depends upon the state of the fiber at successive points reached by the impulse. The impulse resembles a spark traveling actively along a train of gunpowder rather than a wave transmitted passively through air or water. In either of the latter two instances in contrast to the first, the energy is derived from a source other than the medium through which the wave travels and the force and amplitude of the wave become gradually reduced with distance. To carry further the analogy drawn between the impulse and the burning train of gunpowder—if a section of the

powder fuse is dampened in advance of the spark the latter becomes less intense as it passes through the dampened section, and travels more slowly. Upon reaching a succeeding dry portion the spark flares up again to its previous intensity and velocity, and so long as the powder remains dry is transmitted without change to the end of the fuse. In a comparable way, if the activity of a segment of nerve is depressed by treatment in a chamber with a narcotic (alcohol or ether vapor) the

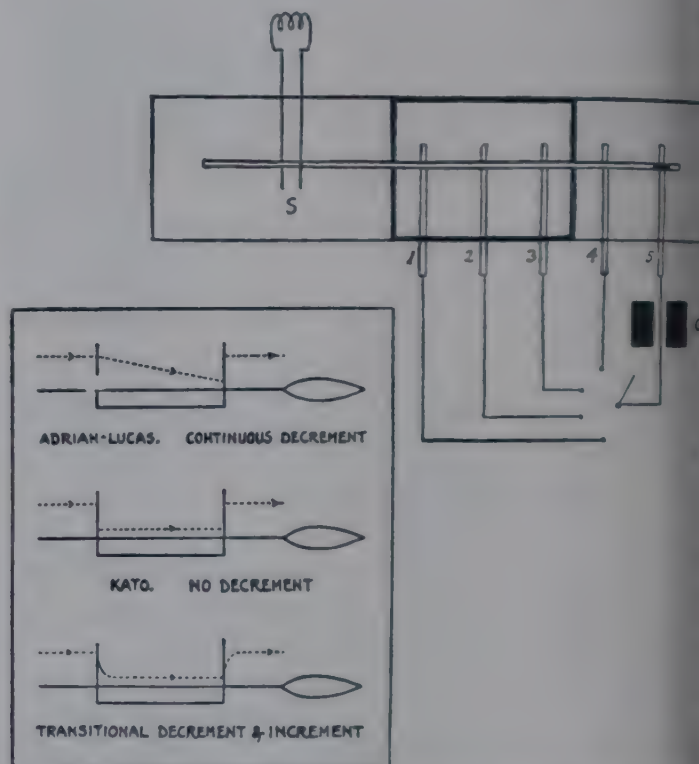


FIG. 318. Upper drawing, diagram of nerve (peroneal of cat) in narcotizing chamber to illustrate experiment of Davis, Forbes and associates. S, stimulating electrode. Leadoff electrodes at 1, 2, and 3 within the chamber, and 4 outside. Circuit completed through an indifferent electrode at 5. G, galvanometer for recording action currents. Nerve in chamber exposed to alcohol vapor. The results of this experiment gave no evidence of conduction with a decrement. The action currents from all three leads within the chamber were reduced to practically the same degree. Lower drawing contrasts the different views advanced regarding conduction of the impulse through a narcotized region of nerve. It will be noted that in all three the impulse regains its full value upon entering healthy nerve (from Davis, Forbes, Brunswick and Hopkins).

impulse undergoes a reduction in amplitude and velocity in its passage through the narcotized region, but upon reaching the untreated nerve beyond, regains its original value, and is transmitted unchanged to the termination of the nerve. The question then arises whether the strength of the impulse in its passage through the narcotized section of nerve is suddenly reduced or whether the reduction is progressive. In other words, would the impulse suffer a greater reduction if it were made to traverse a long section of narcotized

erve than if it passed through a short stretch? Until recently it was thought that a gradual or progressive impairment of conduction, i.e., *conduction with a decrement*, occurred. The propagation of the impulse over narcotized nerve was therefore supposed to be different from that along normal nerve. If the narcotized section were long enough, complete extinction of the impulse would result; in this region, therefore, the impulse would resemble a wave transmitted through air or water. From his experiments, in which the long nerve of the Japanese toad was employed, Kato could obtain no evidence that there was a progressive decline in the strength of the impulse. He came to the conclusion that the impulse suffered instantaneous reduction upon entering the region of narcosis and underwent no further reduction during its transmission along the narcotized section. Conduction was therefore *decrementless*. Kato's findings have been confirmed by Davis, Forbes, Brunswick and Hopkins (see fig. 318) but it is pointed out that on theoretical grounds there must exist a short transitional portion of the nerve at the junction of the normal and the narcotized section, 7 mm. or less in length, where progressive decline in the impulse occurs. Beyond this the impulse is conducted throughout the length of the narcotized section without further reduction.

Conduction rates

The velocity of the nerve impulse varies in different nerve fibers in accordance with their diameters, the thicker fibers conducting more rapidly than those of smaller diameter. In the large motor fibers of the mammal the rate is from 50 to 100 meters per second. Sensory nerves of the skin being of smaller diameter have slower conduction rates. Non-medullated fibers conduct more slowly than medullated. Some of the fibers subserving pain sensation and those of the sympathetic nervous system have a very slow conduction rate (see also p. 802).

The following table from Hill (*Chemical Wave Transmission in Nerve*, Cambridge University Press), gives the conduction rates in the nerves of several different animals.

Medullated nerve, mammal, 37°C., about 100 m./sec.
Medullated nerve, dogfish, 20°C., about 35 m./sec.
Medullated nerve, frog, 20°C., about 30 m./sec.
Non-medullated nerve, crab, 22°C., 5 and 1.5 m./sec.
Non-medullated nerve, mammal, 37°C., about 1 m./sec.

Non-medullated nerve, olfactory of pike, 20°C., 0.2 m./sec.

Non-medullated nerve, in fishing filament of *Physalia*, 26°C., average 0.12 m./sec.

Non-medullated nerve, in Anadon, 0.05 m./sec.

Compare the velocity of sound in air at 0°C., 331 m./sec.

By an indirect method of measurement Carmichael and his associates found the rates of conduction in various human postganglionic sympathetic nerves to be from 0.85 to 2.30 meters per second. The lower figures were obtained for the nerves of the leg, the higher ones for the nerves of the chest.

The "all or none" principle

A stimulus which is just capable of exciting a nerve fiber (threshold stimulus) sets up an impulse which is no different from one set up by a much stronger stimulus. The impulse set up by the weak stimulus is conducted just as rapidly and is just as strong, when judged by the action current developed or the mechanical response of the muscle, as one set up by the strong stimulus. Briefly, the propagated disturbance set up in a single nerve fiber cannot be graded by grading the intensity or duration of the stimulus—the nerve fiber gives a maximal response or none at all. To make use again of the train of gunpowder analogy—the flame of a match applied to the powder fuse will start a traveling spark no less intense than one started by the flame of a torch. The restoration of the strength of the impulse to its original value after passing from a narcotized region into healthy nerve (p. 784) also shows the "all or none" nature of nervous conduction. The well known fact that a strong stimulus applied to a nerve trunk causes an action current of greater amplitude, and a greater muscular response than a weaker stimulus appears to contradict the all or none principle. The nerve trunk, however, is composed of many fibers each of which supplies a group of muscle fibers. The weak stimulus excites only a proportion of the units of the nerve, a maximal stimulus excites them all. For example, the *cutaneous dorsi muscle* of the frog is supplied by a nerve which contains only 8 or 9 fibers; each of these innervates about 20 muscle fibers. Keith Lucas found that when the nerve was stimulated by shocks, gradually increasing in intensity, the muscular responses did not show a similar continuous rise in amplitude; on the contrary, the responses of the muscle increased in a series of well-defined steps; that is, increasing the stimulus intensity produced no effect for a time upon the amplitude of the muscular response, but then a

slight increase in strength of stimulus produced a sudden rise in amplitude. The steps were never greater in number than the number of fibers, and were due, it was concluded, to additional fibers becoming excited as the strength of stimulus reached a certain value.

It must also be remembered that the all or none principle applies only for the condition of the nerve at the point where, and the moment when, the impulse arises. A stimulus which will give rise to a response of a certain magnitude under one condition of the nerve may give a much smaller response under other conditions, e.g., during the relative refractory period, (p. 787), narcosis, oxygen lack, etc.

Variations in the frequency of the impulses in a single nerve fiber

The magnitude of the muscular response is determined not only by the number of neuromuscular units excited but also by the frequency of the impulses transmitted along the individual nerve fibers. When a motor nerve is stimulated maximally by a single induction shock, an impulse passes along each nerve fiber and the "volley" of impulses upon reaching the muscle causes a single contraction of all its fibers—a so-called muscle twitch. If the nerve is stimulated again after a certain brief interval a second volley of impulses is discharged and a second contraction occurs, which becomes superimposed upon the first to produce a greater muscular response. This is spoken of as *summation of contractions*. A series of volleys reaching the muscle at sufficiently short intervals will prevent any relaxation of the muscle between separate volleys. That is, the individual contractions become fused to produce a sustained maximal response or *tetanus*. Adrian and Bronk isolated a single fiber of the phrenic nerve in the cat and recorded the action currents passing along the fiber during normal respiration and after clamping the trachea. The action currents increased in frequency from between 20 and 30 per second during quiet breathing to between 50 and 80 during the forcible respiratory movements induced by the asphyxia. But no change in the amplitude or form of the electrical waves occurred. At the lower rate of discharge the individual contractions were incompletely fused (*incomplete tetanus*). At the higher rates the tetanus was complete and the tension developed by the contraction maximal. It might be thought that when the impulses are of low frequency and there is, in consequence,

incomplete fusion of successive twitches the contractions of a muscle would be uneven and jerky. This would be so did the impulses discharged from the nerve centers travel synchronously along the different fibers composing the motor nerve. At low frequency, however, the impulses are discharged asynchronously, i.e., not as a volley but rather as a scattered fire rifle shots. Groups of muscle fibers are therefore activated asynchronously, the contractions of different groups overlap and a smooth steady contraction of the muscle as a mass results. At high frequencies the impulses are discharged along the separate nerve fibers synchronously, i.e., in series of volleys, but owing to the fusion of the successive contractions the action of the muscle as a whole is also smooth and sustained. Results comparable to those described for the phrenic were obtained from a single fiber of a motor nerve supplying a skeletal muscle (N. to the peroneus longus, to the tibialis anticus or to the quadriceps). A reflex discharge of impulses was produced by stimulation of the foot and the impulses recorded from the motor nerve, all the fibers of which except one had been severed. The impulse frequency varied from 20 to 90 per second with the strength of the stimulus. *The amplitude of the recorded electrical changes was not increased by the strongest stimulation, i.e., the action potential is "all or none in nature."*

By inserting a pair of very closely approximated electrodes into a muscle, it was found possible to record the action currents of a small group of muscle cells supplied by a single nerve fiber (Adrian and Bronk). A fine copper wire (gauge 36), enamelled except for its tip, was passed down a small hypodermic needle. The exposed wire projecting from the point of the needle forms one electrode and is connected to the input of an amplifier. The needle itself constitutes the other electrode and is connected to earth. The action currents may be led, after amplification, to a capillary electrometer or oscillograph and recorded photographically or converted into sound by a loud speaker, their rhythm then being picked up by ear. When the concentric needle electrodes were inserted into the human triceps and a voluntary movement made, the records indicated that the impulses arriving along a single nerve fiber varied with the strength of the contraction from 5 to 50 per second. No electrical changes were observed when the muscle was completely relaxed. At the higher rate the record showed minor waves. These were interpreted as indicating that additional neuro-muscular units also came into action during the stronger contraction. At the lower frequency the active fiber groups are fewer and conse-

quently more widely separated; the electrical responses from neighboring groups therefore do not complicate the electrical record of the group immediately surrounding the electrodes. When certain muscles were excited reflexly, e.g., peroneus longus, tibialis anticus of the rat, there was little evidence that the stronger contraction was due to more fiber groups coming into play, i.e., to impulse discharges over a greater number of motor nerve fibers; the grading of the contraction appeared to be due chiefly to variations in the frequency of the impulses.

The absolute and relative refractory periods of nerve

Within a certain brief interval following the passage of an impulse along the nerve fiber a second stimulus, however strong, is unable to evoke a

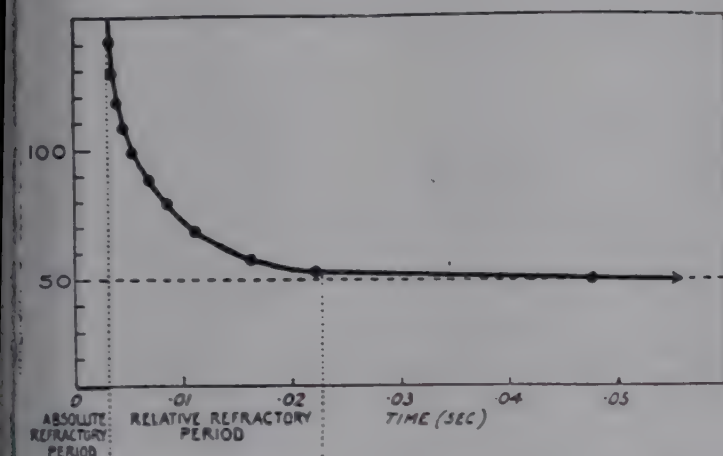


FIG. 319. Curve of the recovery of excitability in the sciatic nerve of the frog. Two stimuli were applied to the nerve, the second stimulus being separated from the first by various time intervals and of just sufficient strength to excite. Intensity of stimulus is plotted along the ordinate, time along the abscissa. The interrupted horizontal line indicates the threshold strength of current required to excite the resting nerve. During the absolute refractory period (about 0.003 sec. in this instance) a stimulus, however strong, will not excite. The excitability returns gradually during the next 0.02 sec. (relative refractory period) (after Adrian)

response. This interval is called the absolute refractory period. In a frog's sciatic nerve at a temperature of about 15°C. the absolute refractory period has a duration of between 2 and 3 sigmas (0.002 to 0.003 second). Its duration is the same or slightly longer than that of the action potential "spike," (see pp. 789-791). It is much shorter in mammalian nerve (about 0.4 sigmas). Succeeding this period of absolute refractoriness is one in which the nerve, though it will not respond to as weak a stimulus as it did before the passage of the impulse, will respond to a somewhat stronger one. The excitability of the nerve gradually increases and the strength of stimulus necessary for excitation becomes progressively less (fig. 319). In the end, the restoration of excitability is

complete and the nerve responds to a stimulus of no greater strength than that which is capable of exciting a resting nerve. This period following the absolute refractory phase and during which the excitability gradually rises to normal is called the *relative refractory period*. It lasts for from 0.01 to 0.02 second or at any rate the excitability of the nerve has returned to about 95 per cent of the resting value by this time. (Full recovery however may not be attained until the lapse of 0.1 second.) It should be pointed out that the failure of the nerve to conduct a second impulse is not due simply to lowered excitability at the *point in the nerve where the original stimulus was applied*, for during the absolute refractory period a stimulus applied to any other point upon the nerve likewise fails to set up an impulse. The passage of the impulse along the nerve leaves in its wake a change of state like a trail of ash after the ignition of a powder fuse. For the moment the impulse consumes the entire resources of the nerve fiber (Adrian). The burned fuse must have its store of energy replenished by laying a fresh train of powder grains before a second spark can traverse the path of the first. So also, a certain time is required for the changes associated with the passage of the impulse to become reversed and the nerve restored to its resting condition (polarized state, see also p. 791).

The refractory period renders a continuous excitatory state of the nerve impossible just as the corresponding period in cardiac muscle assures rhythmical contractions and prevents summation and tetanus. The propagated disturbances resulting from repeated stimulation of the nerve fiber may be compared to a stream of bullets rather than to a stream of water. Fusion or summation of impulses does not occur. The refractory period obviously must also limit the frequency of the impulses. In the mammal the absolute refractory period is about $\frac{1}{1000}$ second. The intervals between impulses, obviously, cannot be shorter than the absolute refractory period; the maximum impulse frequency is therefore around 1000 per second. At this rate the impulses are travelling into the *relative* refractory period of their predecessors and are consequently weaker. In frog nerve with its refractory period of from 2 to 3 sigmas, the maximal impulse frequency is between 250 and 300 per second.

THE SUPERNORMAL AND SUBNORMAL PHASES. The relative refractory period is succeeded by one lasting for from 3 to 15 sigmas, in which the nerve fiber is

hyperexcitable. This is followed in turn by a state of subnormal excitability which persists for from 15 to 70 sigmas.

THE ELECTRICAL CHANGES IN NERVE

The current of injury

When a pair of electrodes are placed a short distance apart upon the surface of an uninjured and resting nerve (or muscle) and connected through a galvanometer, no current flows and no deflection of the instrument occurs, since the entire surface of the nerve (or muscle) is positively charged. When, however, one part of the tissue is injured the membrane at this point becomes depolarized (see membrane theory, p. 791) and, in consequence, negative to the positively charged uninjured surface. When the two electrodes are now placed one on the injured and the other on the uninjured part and connected through a galvanometer a constant current flows through the instrument from the uninjured (+) to the injured (-) section and in the opposite direction through the length of the tissue. This is known as the *current of injury* (or *demarcation current*) (fig. 320, I).

The current of action

Active tissue is also relatively negative to resting tissue. The former corresponds to the zinc or negative pole of a battery, the latter to the copper or positive pole. If, therefore, two electrodes are placed upon a section of nerve and connected through a galvanometer, as shown in fig. 320 II, A, stimulation of the nerve at S causes a movement of the galvanometer indicator first in one direction and then in the other. The movement may be photographed, when a diphasic curve—a wave above the base line followed by one in the opposite direction—is obtained. This is the result of the propagation of the wave of excitation along the nerve from one electrode to the other. When the wave reaches the tissue beneath the first electrode this region becomes negative to the resting tissue beneath the second electrode. A current flows through the galvanometer from the resting to the active region. A wave above the base line is inscribed in the record (fig. 320 II, B). During the lapse of time from the passage of the wave from beneath the first electrode to its arrival at the second no current flows, and the galvanometer indicator returns to the zero position (fig. 320 II, C). The arrival of the excitation wave beneath the second electrode

now renders the tissue here negative to the tissue under the first electrode, and a current through the galvanometer, but in a direction opposite to that of the current previously seen. As the nerve beneath the second electrode returns to the inactive state the galvanometer comes to rest. A wave below the base line is thus recorded (fig. 320 II, D and E). The diphasic electrical change is called the *current of action*. If a current of injury is set up by crushing the nerve between the second electrode stimulation of the nerve beyond the first electrode sets up an action current.

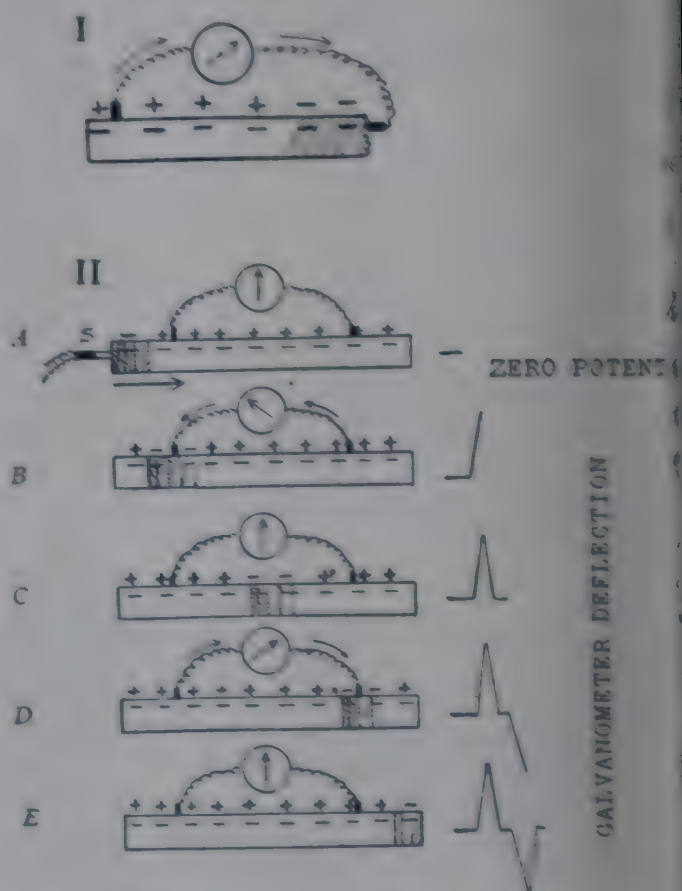


FIG. 320. I, current of injury; II, current of action. Description in text. The small arrows indicate flow of the current in the galvanometer leads; the arrow, in II A, indicates the direction of spread of wave of contraction.

which, being in the opposite direction to current of injury, causes this to be reduced. This reduction in the strength of the current of injury causes a movement of the galvanometer indicator toward the zero position; this is spoken of as *negative variation*. The excitation wave does not reach the tissue beneath the second electrode so it is blocked by the injured tissue so a second oppositely directed wave does not appear, i.e., variation is *monophasic*.

So far as is known the propagated disturbance in nerve is invariably accompanied by an electrical change. In fact there is no evidence to indicate

the nerve impulse and the traveling electrical wave are not one and the same. At any rate they are very intimately related and the investigation of the electrical changes in the nerve fibers by the method of recording is therefore the most convenient and at the same time the most sensitive and accurate means we possess for studying the frequency, speed and strength of the nerve impulse. For example, the number of successive electrical impulses traversing the nerve is taken as representative of the frequency of the impulses; the speed and amplitude of the impulse is judged from the speed and amplitude of the electrical response. The action waves are of the same general form in all types of nerve fiber; this is taken as an indication that the impulses in the different nerve fibers are fundamentally similar.

After-potentials. Following the main action potential, called the "spike" potential as it is now usually called, a number of smaller electrical changes appear in tracings obtained by the more sensitive methods of recording. These are known as *after-potentials*. They appear as a series of spikes, but in their simplest form, as a single response. They consist of an initial negative potential (i.e. of the same direction as the action potential) followed by a positive deflection of much smaller amplitude (about 0.2 per cent of the height of the action potential) but of longer duration. The negative after-potential has a duration in rapidly conducting fibers of about 15 μ , the positive after-potential of one second or more. The after-potentials show much greater variability with experimental conditions than does the action potential. A tetanizing current increases both negative and positive after-potentials; with such a current a second negative potential frequently appears which may last several minutes. The spike coincides approximately with the absolute refractory period, the negative after-potential with the supernormal and the positive after-potential with the subnormal phases of excitability, respectively.

The "spike" and the after potentials can also be recorded from the spinal cord during stimulation of a nerve root. The spike potential arises from the stimulation into the cord of the fibers of the dorsal root. Gasser concludes for several reasons that the after-potentials are derived from internuncial neurons.

Compound nature of the action current recorded from a nerve trunk

Langley, Bishop and Gasser studied the action potential of mixed nerve trunks by means of the cathode ray oscillograph.

Like any instrument previously employed for this purpose, e.g., the string galvanometer or the capillary electrometer, the moving part of this instrument—a stream of electrons—possesses practically no mass and

is in consequence inertialess. It is therefore capable of recording almost infinitely rapid changes in electrical potential. The instrument consists of an evacuated tube through which the electron stream is thrown against a fluorescent screen upon which it produces a spot of light. On either side of the electron stream is placed a vertical plate. A potential difference is created between the pair of plates; the electric field thereby set up across the path of the stream deflects it horizontally. By means of a rotating commutator the deflections are repeated 10–20 times per second. The spot of light is thereby converted into a horizontal streak. A second pair of horizontal plates is placed one above, the other below, the electron stream. These are connected with the nerve whose action current is timed to reach them at the instant that the stream is deflected horizontally by the vertical plates. An upward deflection of the electron stream results with the production of a standing wave. This is photographed. The speed of the horizontal movement of the spot of light enables the time factor to be calculated, and can be varied by changing the distance between the pair of plates; the horizontal movement corresponds to the movement of a kymograph, though of course its rate is very many times faster. The upward deflection is analogous to the rise of a muscle lever. The magnitude of the action potential is determined from the height of the wave. Before reaching the recording system the action current is amplified several thousand times by passing it through a three-stage amplifier.

In a mixed nerve the wave of action potential ("spike"), which by slower methods of recording appears simple, has been shown in reality to be compounded of three waves differing from one another in amplitude and conduction rates. They have been designated, respectively, *alpha*, *beta* and *gamma* waves (fig. 321). For example, when the potential changes are recorded as 12 mm. from the point of stimulation the wave is simple; at 31 mm. its descending limb shows a hump. At 46 mm. two waves may be distinguished from the main wave which is now considerably reduced in amplitude. At 82 mm. three separate waves are clearly seen. The three waves may be compared to runners in a race who, though starting together, gradually become scattered as the faster contestants outstrip the slower. In the dog's sciatic nerve the alpha wave has a speed of about 90 meters per second, and the beta and gamma waves 50 and 30 meters per second respectively. The three types of wave have the same general form but the alpha wave has a greater amplitude than the others; the gamma wave is the smallest. Through histological counts of the fibers of different sizes in the mixed nerve the respective action waves have been identified with fibers of

different diameters. In the peroneal nerve of the frog, for instance, there are three groups of myelinated fibers whose diameters are around 16, 10 and 5 microns, respectively. The fibers of largest size (16 microns) are responsible for the *alpha* wave, the intermediate and the smallest fibers give rise respectively to the *beta* and *gamma* elevations. That is, the larger the fiber the faster its conduction rate. The excitability and length of the refractory period of the fiber also varies with the diameter, the smaller ones possessing a higher threshold and a longer refractory period than the larger.

A correlation has also been established between fiber size and the action potential wave, on the

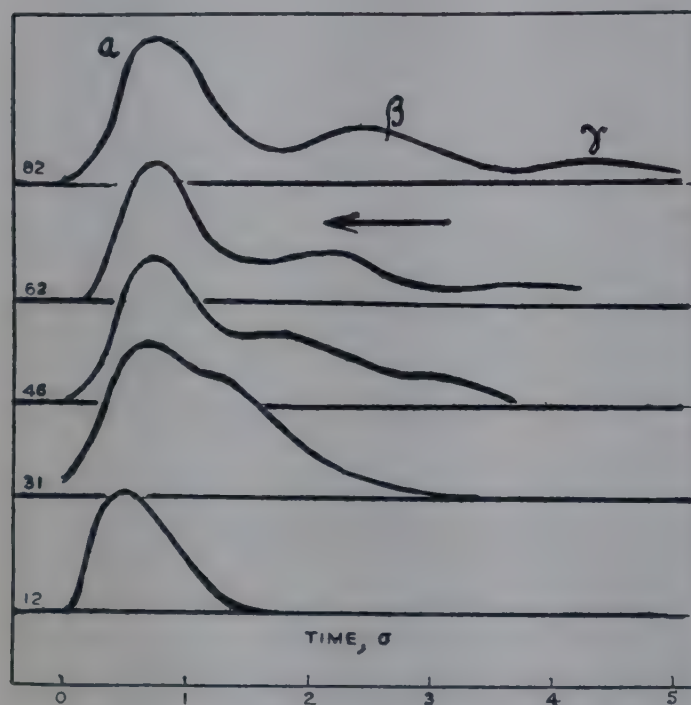


FIG. 321. Cathode ray oscillograph records of the action currents in the sciatic nerve of the bullfrog after conduction from the point of stimulation through the distances (in millimeters) shown at the left (see text) (modified from Erlanger, Bishop and Gasser).

one hand, and the function and course or distribution of the fibers on the other. When the peripheral end of the sciatic was stimulated and the action current recorded from one of the anterior roots of the nerve, only the *alpha* wave appeared. All three waves, however, can be recorded from the sensory root. It is therefore concluded that the large efferent and afferent fibers of the mixed nerve give rise to the *alpha* wave. The *beta* and *gamma* waves are due to action potentials arising solely in afferent fibers.

When a *motor* branch of the femoral nerve of the dog is stimulated and the action potential led from the trunk of the nerve, only *alpha* waves are obtainable as in the case of the anterior root.

Stimulation of a branch of the nerve going to the skin (saphenous) gives *beta* and *gamma* waves but not the *alpha* elevations. It is evident from the preceding nerve-root experiments that the *alpha* waves are produced in the large efferent (motor) and afferent fibers (muscle-sense) of the muscular branch and that the *beta* and *gamma* waves are developed in afferent fibers subserving skin sensations.

The fibers responsible for the three waves α , β , and γ , just described are now referred to as the *A* group, since later work of Erlanger and Gasser has revealed the existence of two other groups of peripheral nerve fibers of slower conduction rate, lower excitability, and which give rise to action potentials of much smaller amplitude. When a stimulus considerably stronger than one required to excite the *A* group is applied to the mixed nerve and the amplification of the instrument increased, the elevations due to the excitation of these fibers appear. The fibers are referred to as the *B* and *C* groups respectively. When the action potential was recorded from the nerve at a distance of 9 mm. from the point of stimulation, the first of these waves, designated *B*, appeared about 15 σ after the crest of the *gamma* wave of the *A* elevation. The second wave, designated *C*, appeared about 110 σ after the termination of *B*. The *B* elevation is also sometimes, like the *A* elevation, compound and the *C* elevation usually so. The fibers giving rise to the *B* elevation have conduction rates midway between those given by the slowest fibers of the *A* group and those given by the *C* group. In the dog the rates of the *B* group vary between 10 and 20 meters per second; those of the *C* group between 0.3 and 1.6 meters per second. The *B* fibers are excited by a weaker stimulus than that necessary to excite the *C* group and both groups as already mentioned have a higher threshold than the *A* group.

To sum up:

The *A* group of fibers consists of: (a) Large efferent (motor) and afferent (muscle sense) fibers of the mixed nerve which are responsible for the *alpha* wave. (b) Afferent cutaneous fibers (touch and temperature) which are responsible for the *beta* and *gamma* waves.

The *B* group, i.e., those responsible for the *B* elevation, enter the mixed nerve through the gray rami communicantes. They are evidently post-ganglionic sympathetic fibers.

Fibers belonging to the *C* group are found in: (a) Anterior roots and white rami. These are

fferent and myelinated (pre-ganglionic sympathetic fibers). (b) Gray rami. (c) Posterior roots. These are afferent and non-myelinated. They possibly transmit sensations of pain.

B and C types of fibers are found in both autonomic and muscular nerves.

It is impossible to identify the C and B groups of fibers by means of fiber diameter or structure since

It has been suggested that the non-myelinated C fibers of the posterior root subserve protopathic sensibility (p. 803), while epicritic impulses are conveyed by certain fibers of the A group.

THE MEMBRANE THEORY OF NERVOUS CONDUCTION

Conduction, according to this theory, is a surface phenomenon. The nerve fiber is surrounded by a semi-permeable membrane or surface

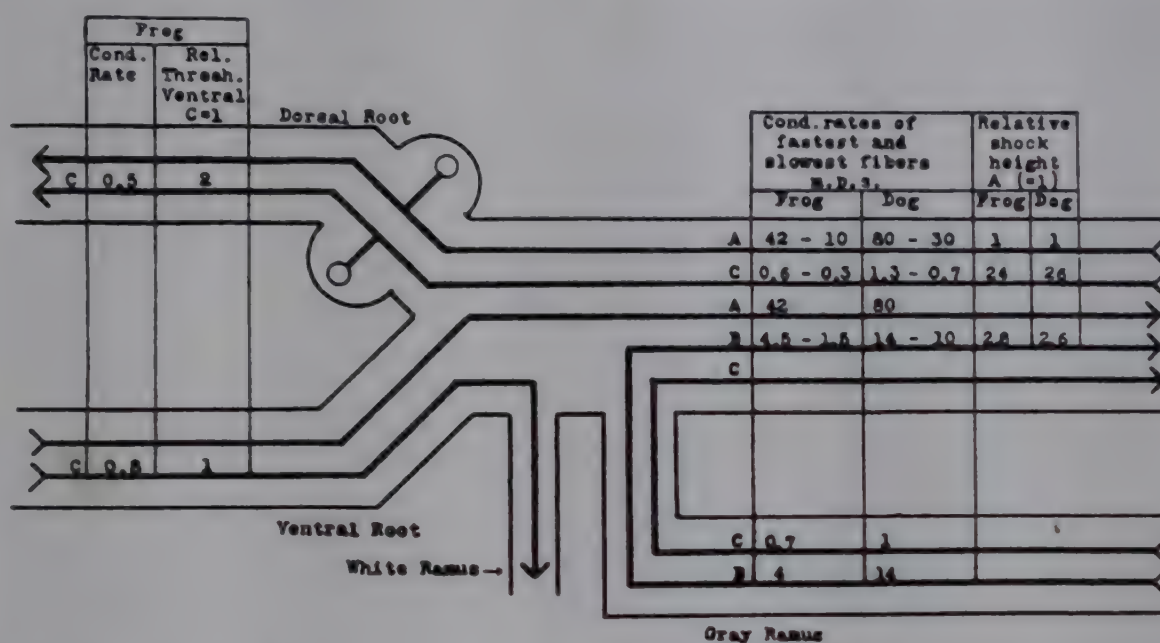


FIG. 322. Diagram indicating the sources and a typical set of reactivities of the fiber groups that contribute to the action potentials of mixed nerve and spinal roots (after Erlanger and Gasser).

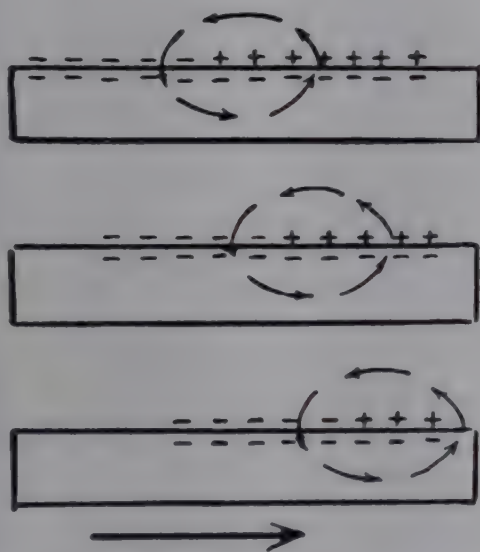


FIG. 323. Illustrating nervous conduction according to the membrane theory (see text).

There is not the correlation between fiber size and conduction rates that is seen in the case of fibers making up the A group. For instance, the very slowly conducting C fibers of the anterior roots and white rami are relatively large, having diameters of 4μ or more. Furthermore, though all the A fibers are myelinated the C group, as pointed out above, may be either myelinated or non-myelinated. The distribution of the different fiber groups are summarized in the following scheme (fig. 322) from Erlanger and Gasser.

film which is polarized when the nerve is at rest. That is, the surface film separates a layer of cations on its outer side from a layer of anions on its inner side. A stimulus applied to the nerve increases the permeability of the membrane at the point of stimulation with the result that a redistribution of ions and depolarization of the membrane occurs. This point of the nerve becomes thereby relatively negative to the inactive (polarized) section of nerve immediately adjacent. A potential difference is set up and a current flows between the active and inactive sections. This secondary current in turn causes depolarization and activation of the adjoining region which, being now relatively negative to the next section results in a current being again set up between these two which depolarizes the latter. Thus the currents set up between contiguous, inactive and active regions serve as successive stimuli and the wave of depolarization spreads down the nerve; the disturbance set up by the original artificial stimulus is in this way propagated automatically (see fig. 323). The depolarized state persists for a short time after the passage of the impulse; during this time the nerve is refractory. The return of

excitability is dependent upon the restoration of the polarized state.

Perhaps the greatest support for the membrane theory is afforded by the experiments of Lillie who has prepared a metal model which behaves in a manner comparable to that of nerve. A film of oxide forms upon an iron wire placed in strong nitric acid. When such an oxide-coated wire is then immersed in a weak solution of acid, which would cause gradual solution of an untreated wire, no reaction results. The metal is in a so-called passive state, being comparable to a resting nerve. When, however, the wire is "stimulated," e.g., touched at one point with active iron or some other base metal, scratched with a piece of glass in order to break the protective oxide film, or an electric current applied to it, a reaction (electro-chemical reduction) is set up which, accompanied by effervescence and the formation of a dark-colored lower oxide, sweeps down the wire. If two parts of the wire be connected with a galvanometer a current flows through the instrument during the spread of the reaction. If the acid bathing the wire is of a certain concentration, the protective film reforms in the wake of the reaction. If a second "stimulus" is applied after the film has reformed, but not before, a repetition of the phenomenon occurs. The resemblance of the reaction of the iron wire to the nerve impulse is very striking. Both are electrical in nature; the film of oxide is analogous to the surface film postulated for the nerve fiber. So long as the protective oxide is intact a potential difference exists between the wire on the inside and the surrounding acid. Discontinuity at any point in the film causes this region to become negative to other regions and a wave of depolarization is propagated to the end of the wire.

In its behavior the wire model shows the following remarkable resemblances to that of nerve.

(1) The rate of propagation of the reaction is of the same order as that of the nerve impulse.

(2) The "stimulus" must be of a certain intensity (threshold). A stimulus greater than the threshold causes no greater effect ("all or none" principle).

(3) The wire, as already pointed out, is irresponsive for a short time after the reaction has passed (absolute refractory period); while the film is reforming the reaction is set up with greater difficulty (relative refractory period).

(4) When an electric current is employed to activate the wire it must rise to its maximal intensity rapidly in order to elicit the reaction.

(5) The activating current must flow for a certain minimal length of time (chronaxie) in order to produce the effect.

In the wire model a demonstrable temporary break in the continuity of the oxide deposit is produced. It is presumed that the excitation of nerve is associated with a corresponding change (increase in permeability) in the surface film surrounding the nerve fiber. Though

such a permeability change has been demonstrated in certain slowly conducting protoplasmic systems, evidence for its occurrence in nerve is indirect. In the case of nerve and other protoplasmic systems alteration in permeability is associated with chemical changes—the processes underlying the excitation of nerve and the transmission of the impulse are therefore as in the case of the iron wire model, essentially electrochemical in nature.

METABOLISM OF NERVE AND BRAIN

It has been thought until comparatively recent years that a negligible expenditure of energy accompanied the transmission of the nerve impulse.



FIG. 324. Diagrammatic representation (not to scale) of the heat production due to each nervous impulse, indicating how the observed heat resulting from a tanic stimulation is built up of these units. The horizontal lines represent the delayed heat, starting at a maximum rate of 0.05 "C" units and slowly falling to zero in about 10 mins. The vertical lines represent the initial heat which probably is largely produced during the first 4σ at a rate 5000 times greater than that at the start of the delayed phase (after Gerard).

the latter was believed to be dependent upon physical rather than upon chemical processes. Though it had been recognized that conduction eventually failed in the absence of oxygen, the fact did not prove that conduction itself was due to oxidative processes. In order to show this would be necessary to demonstrate an increase in the oxygen consumption and in the carbon dioxide production during activity. An increase in carbon dioxide production of active nerve over that of resting nerve was observed by Tashiro in 1913. This was confirmed by Parker, and increased oxygen consumption during excitation was shown by Fenn. Earlier attempts to demonstrate heat production in active nerve were unsuccessful, but in 1926 Hill, using a thermopile composed of over two hundred thermocouples,

ected a rise of $\frac{7}{10,000}^{\circ}\text{C.}$ in the temperature of nerve as a result of stimulation lasting 10 seconds.

HEAT PRODUCTION IN NERVE

The resting sciatic nerve of the frog in oxygen liberates about 70×10^{-6} calories³ per gram of nerve per second. In nitrogen the resting heat production falls gradually to about 25 per cent of this value. During stimulation in oxygen, at the rate of 280 shocks per second, an increase in heat production occurs of 40×10^{-6} calories per gram of nerve per second. At this rate of stimulation the heat resulting from a single impulse is about $40 \times 10^{-7} \frac{14}{100,000,000}$ calories per gram of nerve fiber. The heat production of nerve during activity is only about $\frac{1}{400,000}$ of that produced in an equivalent weight of muscle stimulated to the same degree.

As in the case of muscle the heat is given off in two phases—the *initial heat* and the *delayed* or *recovery* heat. The initial heat is, however, less than 10 per cent of the total heat,⁴ the ratio of initial to delayed heat being 1:9 as compared with 1:1.24 in the case of muscle heats. The rate of generation of the initial heat is some 5000 times greater than that of the delayed heat. The former lasts for only a few thousandths of a second, being an intense explosive outburst as compared with the slowly developed but greater delayed heat (p. 324). The delayed heat is accompanied by the consumption of oxygen and is evolved in two stages. The first of these lasts for a few seconds, and the quantity of heat is of small magnitude; the second lasts for 10 to 30 minutes and contributes the greater portion of the delayed heat.⁵ Increase in the length of the stimulus does not increase the heat production, whereas increase in the frequency of stimulation causes an increase in heat production up to 100 per cent. The heat per second, however, does not increase proportionately with the increase in frequency of stimulation, so the heat per impulse is actually reduced. When the shocks are at the rate of 280 per second the heat production per second is maximal and the heat per impulse (since each impulse is travelling

in the relative refractory period of its predecessor) is only a quarter of that generated by a single isolated impulse. The heat production of the central nervous system is enormously greater than that of nerve fibers amounting to from 600 to over 2000×10^{-6} per gram per second for the spinal cord of the frog.

CARBON DIOXIDE PRODUCTION AND OXYGEN CONSUMPTION

The resting sciatic of the frog produces in the neighborhood of 0.6 cu. mm. CO_2 per gram of nerve per minute. The corresponding O_2 consumption is about 0.7 cu. mm. The resting respiratory quotient is therefore around 0.8. During activity an extra 0.25 cu. mm. of O_2 per gram of nerve per minute is consumed and a somewhat smaller quantity of extra CO_2 produced. The extra metabolism of the nerve resulting from activity has an R.Q. of about 0.90 (Meyerhof and Schmidt).

The extra oxygen consumed by the nerve resulting from activity occurs during the period of delayed heat. It continues for a considerable time—15 minutes or more after the impulse has passed. The quantity of oxygen consumed agrees well with the heat produced at this time, upon the basis that the latter is the result of the oxidation of ordinary food materials. Like the heat production the oxygen consumption per impulse falls with a rise in frequency of stimulation, though of course the total consumption per minute increases. Increasing the strength of the stimulus beyond that necessary to excite all the fibers does not increase the oxygen consumption.

CHEMICAL CHANGES

(a) IN THE ABSENCE OF OXYGEN. Placed in nitrogen a *resting* nerve undergoes a reduction in its glycogen and free sugar contents and an accumulation of lactic acid. The lactic acid production proceeds slowly and in about 3 hours has reached a maximum rate of 7 mg. per 100 grams of nerve per hour; it then falls gradually to zero. The total acid production is about 100 mg. per 100 grams of nerve (0.1 per cent). This is not attained until the end of 24 hours, at which time the carbohydrate store of the nerve becomes exhausted. Immersion of the nerve in a solution of glucose (but not of galactose or fructose) causes lactic acid production to continue at the maximum rate (7 mg. per cent) for days—or until conversion of the added glucose has occurred. When the nerve is *stimulated* in nitrogen there does not result, however, as in the case of muscle deprived of

³Small calories.

⁴Hill found that the initial heat of crustacean nerve is only 2.25 per cent of the total heat, which, however, is much greater (215×10^{-3} per second per gram of nerve) than that of frog nerve. Beresina and Feng obtained similar values for crab nerve.

⁵The cause of the initial heat is unknown. It may be of chemical in nature and due to the breakdown of phosphocreatinine or may be derived, as Hill suggests, from an electrical source, namely, the discharge of an electric double layer—a condenser—located at the surface of the fiber. See A. V. Hill, "Chemical wave transmission in nerve." Cambridge, University Press, 1927.

oxygen, an increased accumulation of lactic acid. Also when oxygen is re-admitted lactic acid does not disappear or does so very slowly. Oxygen consumption of the nerve is somewhat greater than usual after a period in nitrogen—an indication that nerve runs into debt for oxygen during a period of anoxia. In the absence of oxygen, nerve, unlike muscle, continues to respond to stimulation for a considerable time. It shows a progressive fall in excitability but does not fail to conduct until the lapse of about 3 hours. The action current or the current of injury gradually decreased during this time but rises again when oxygen is re-admitted. A fall in phosphocreatine content and a rise in inorganic phosphorus also occur.

In the asphyxiated nerve the delayed heat production declines no more rapidly (if anything less so) than the initial heat, whereas in the case of a muscle contracting in the absence of oxygen most of the recovery heat is abolished (p. 618). In nerve, therefore, *both conduction and the recovery process can apparently be accomplished for a time after the external oxygen supply has been cut off.*

(b) IN THE PRESENCE OF OXYGEN. In the case of the excised *resting nerve* free sugar gradually disappears but the glycogen content remains unchanged and *no lactic acid is formed*. These observations indicate that the function of the resting nerve is probably maintained in part by energy derived from the combustion of sugar. Energy is also probably derived from the breakdown of phospholipins. *During activity* phosphocreatine is broken down but the glycogen content of the nerve remains unaltered. Sugar does not disappear more rapidly than during rest, nor is lactic acid produced. The glycogen-lactic acid cycle which is so prominent in the metabolism of muscle therefore appears to play no part in nerve fiber conduction. The immediate source of the energy for conduction is believed to be derived from the breakdown of phosphocreatine which is resynthesized after the passage of the impulse. The ultimate source of the energy for the recovery process in nerve is unknown.

It has been thought that the nerve fiber was incapable of oxidizing lactic acid or of synthesizing lactic acid to glycogen, but, as mentioned above, when an accumulation of lactic acid occurs as a result of asphyxia small amounts do disappear upon the re-admission of oxygen. Also, in a nerve soaked in sodium iodoacetate the phosphocreatine disappears and the nerve soon fails to respond, but if lactate be supplied the survival time is considerably lengthened and

oxygen consumption increased (Feng). (The addition of lactate causes no increased oxygen consumption in normal nerve.) These and other observations indicate that the inability of the nerve to oxidize lactic acid is not absolute but that, under certain circumstances at any rate, such does occur.

Small quantities of *ammonia* (about 0.3 mgr per cent per hour) are produced by resting nerve and about double this amount during activity. The source of the ammonia is probably adenylypyrophosphate. The *inorganic phosphate* also increases during activity as a result of the breakdown of phosphocreatine and adenylypyrophosphate and, possibly, of phospholipins.

Potassium of nerve. The nerve fiber is exceptionally rich in potassium; Cowan found that the potassium concentration in the nerve of the crab is some 13 times greater than that in crab's blood. But when the nerve is stimulated or deprived of oxygen, potassium diffuses rapidly into the surrounding fluid, but is restored again during rest or in the case of the asphyxiated nerve, after the readmission of oxygen. A nerve at rest and adequately supplied with oxygen does not lose potassium and a potential difference between the surface of the fiber and its interior is maintained. Increasing the concentration of potassium in the fluid bathing the nerve will tend to reduce the potential difference; this procedure also reduces the excitability of the nerve and with high concentrations excitability is completely lost but is restored again when the nerve is placed in sea water. The amplitude of the action current or of the current of injury is also markedly reduced by raising the potassium concentration on the outer side of the nerve. Furthermore, when the nerve is exposed to cold, "blocking" of the impulse occurs at a higher temperature than usual if the nerve has been soaked in a solution containing a high percentage of potassium. Finally, a high concentration of this cation in the fluid in which slices of brain tissue are immersed, greatly increases the production of lactic acid from glucose in the presence of oxygen; in an atmosphere of nitrogen, on the other hand, lactic acid production is depressed by potassium.

These several observations have no doubt shown the importance of potassium in nervous activity but they give little precise information concerning the rôle which it plays. The outward diffusion of K ions is apparently an essential factor in the development of the potential change associated with the conduction of the nerve impulse.

The metabolism of the resting nerve may be considered in terms of the membrane theory (p. 791) to be directed toward securing a certain degree of impermeability of the surface film for the maintenance of the polarized state. The chemical changes associated with activity result in increased permeability and depolarization. During recovery the membrane is repolarized, the energy being furnished by oxidative processes—the battery is recharged. The source of the energy which enables a nerve to continue to conduct for such a long time in an atmosphere of nitrogen is a matter for speculation. The energy for the recovery of the fiber between impulses may be derived from the reduction of hydrogen acceptors in the nerve substance, which thus serve as oxidizing reserves when oxygen is excluded. It has been shown, for example, that a hydrogen acceptor such as *metadinitrobenzene* is able to restore conduction in an asphyxiated nerve (Cohen and Gerard). This substance will also restore motility to asphyxiated spermatozoa. Sodium peroxide and hydrogen peroxide are also capable of restoring the power of conduction in asphyxiated nerve. When, as a result of prolonged stimulation in nitrogen, the oxidizing reserves become exhausted recovery of the nerve cannot be accomplished since energy for the repolarization of the membrane is not available, and conduction fails.

The *brain* (gray matter) when supplied with oxygen oxidizes glucose and, unlike the nerve fiber under the same conditions, produces lactic acid, though in small amounts. Lactic acid is also produced slowly when glucose is added to brain slices *in vitro*. Large quantities of lactic acid are formed, however, by the brain under anaerobic conditions. Glucose is present in brain tissue in about the same concentration as in blood, and is the main substrate for the respiration of the gray matter. The respiratory quotient of the brain is around unity. The gray matter contains only small amounts of glycogen. When the latter is added to brain slices it is broken down very slowly to lactic acid. Hexosephosphate, according to Ashford and Holmes, is not an intermediary in the oxidation of glucose by brain tissue, but the production of pyruvic acid appears to be an essential step. The utilization of glucose by brain tissue is made evident by its addition to brain slices, an increased consumption of oxygen then occurs. The oxygen consumption of brain tissue *in vitro* is also increased by the addition of mannose, fructose, pyruvate or lactate. The large production of lactate under anaerobic conditions and the minimal amounts produced when the oxygen supply is adequate raises the question whether the formation of lactic acid plays any role in the

normal function of the brain. It appears, at any rate, that it does not play an indispensable part in the oxidation of glucose, for nicotine, iodoacetate or hydroxymalonate inhibits the oxidation of lactate but permits glucose to be oxidized. Though lactate is utilized by the brain, glucose appears to be the main source of energy. A respiratory quotient of unity supports the conclusion that the main fuel of the brain is carbohydrate, but more direct evidence for the oxidation of glucose can be cited. Himwich and Fazekas, for example, determined the glucose and oxygen contents of the arterial blood and of blood drawn from the superior longitudinal sinus of anesthetized dogs. They obtained a figure of 13 mg. per 100 cc. of blood for the glucose utilization. The quantity of oxygen which by calculation would be required to oxidize this quantity of glucose is 9.7 cc. The oxygen consumption actually observed was 9.3 cc. Chute and Smythe found that the isolated surviving cat's brain perfused with defibrinated blood used from around 100 to 400 mg. per gram of brain tissue per hour and from 40 to 120 mg. of lactate per gram per hour. There appeared to be a direct relationship between the level of the blood sugar and the quantity of glucose used. In the same preparation the oxygen consumption (calculated from the arterio-venous oxygen difference and the cerebral blood flow) amounted to from 200 to 300 cc. per 100 grams of brain tissue per hour (see also p. 291). These figures are, of course, for the brain as a whole; the gray matter shows a much higher oxygen consumption than does the white matter which is composed mainly of nerve fibers. It has been estimated that the human brain accounts for from 8 to 10 per cent of the basal metabolism, yet mental work increases the basal metabolism to a negligible extent (p. 536). Though the nerve fiber can contract a small oxygen debt the gray matter cannot, and is, in consequence, highly susceptible to deprivation of oxygen. This is especially true of the higher centers. The delirium of pneumonia is due largely to anoxia rather than to toxemia, and the mental aberrations associated with high altitudes are well known. The metabolism of the cerebellar cortex, according to some investigators, is higher than that of the cerebral cortex. Himwich and Fazekas have made the interesting observation that in week-old puppies the medulla and midbrain have a higher oxygen consumption than has the cerebral cortex but the reverse relationship holds true in adult

dogs. The increased oxygen consumption of the higher centers of grown animals is due presumably to their having acquired greater functional importance and assumed a position of dominance over the lower centers.

The brain is also very sensitive to a reduction in its supply of glucose, and when the blood sugar level falls to a certain point, mental confusion, muscular incoordination, convulsions and loss of consciousness result. The hypoglycemic symptoms are quickly relieved by the administration of glucose, mannose or fructose, but not by pyruvate or lactate. In the human subject insulin hypoglycemia greatly reduces the oxygen consumption of the brain, but this is quickly restored to normal by the injection of glucose (Himwich and associates). The reduction of the metabolism of the brain and its restoration to normal are closely associated in time with the hypoglycemic symptoms and their relief. Lactate and pyruvate have little effect in raising the oxygen consumption above the low level caused by hypoglycemia. It is quite evident from these facts and other observations already mentioned that glucose plays a very special and vitally important part in the metabolism and functions of the brain.

As might be expected from the relationship between the blood glucose level and the oxygen consumption, the effects of anoxia and of hypoglycemia are in certain respects closely similar, and are supplementary to one another. Hypoglycemic convulsions are induced more readily in

the presence of anoxia, and the effects of the latter are more severe if the blood sugar is depressed.

There is no evidence that the lipids—*cholesterol*, *lecithin*, *cephalin* and *sphingomyelin*—which enter so largely into the composition of brain substance serve any special metabolic need; their function is probably to insulate neighboring nerve fibers from one another.

Quastel and associates as a result of their experiments advance the theory that anesthetics and narcotics bring about unconsciousness by inhibiting the dehydrogenase systems of the brain. They found that the addition of glucose or lactate to chopped brain tissue in the presence of an anesthetic alone was followed by an increased oxygen uptake. After exposure of the brain tissue to anesthetics or narcotics (barbiturates, chloroform, hyoscine) the oxygen uptake was much reduced. However, no doubt has been expressed that anesthetics and narcotics in the dosage ordinarily employed exert their effects in this manner. The majority of the drugs investigated cause the mobilization of the carbohydrate stores through the discharge of adrenaline with consequent reduction in brain carbohydrate and a rise in blood sugar. The reduced respiratory rate demonstrable in brain tissue excised from anesthetized animals and compared with that of controls is attributed to their relatively low carbohydrate content rather than to depression of the action of respiratory enzymes (Emerson).

See also action of vitamin B₁, p. 641.

CHAPTER LXIV

THE REFLEX ARC. RECEPTOR ORGANS. CUTANEOUS AND KINESTHETIC SENSATIONS

The involuntary muscular contraction which results from the stimulation of a sense organ is known as a reflex. The quick withdrawal of the hand from some agent which has inflicted pain or the contraction of the pupil when a light is thrown into the eye are familiar examples of reflex action. The activities of various glands are also largely reflex in nature as are many of the reactions of the vascular, respiratory and digestive systems. The exciting cause of the reflex may make an impression upon consciousness, as when a group of skeletal muscles contracts as a result of a painful stimulus; or, as in the case of reflexes involving the secretion of glands or the activities of smooth muscle, e.g., of the blood vessels, heart or digestive tract, the initiating stimulus as well as the reflex act itself may be entirely unperceived.

THE REFLEX ARC

The anatomical basis of reflex action is the reflex arc which in its simplest form consists of:

(a) *An afferent limb* composed of the *receptor organ*, which upon excitation, gives rise to the impulse, and the *neuron* whose processes (central and peripheral) transmit the impulse to the central nervous system. In the case of the spinal reflex arc the cell bodies of the afferent neurons are situated in the posterior root ganglia.

(b) *An efferent limb* constituted of a motor or secretory neuron which conducts impulses from the central nervous system to an *effector organ*—muscle or gland. In the case of motor spinal reflex arcs, the axons of the efferent neurons leave the cord by the anterior nerve roots and travel in the peripheral nerves; their cell bodies are situated in the anterior horns.

(c) *A center* situated in the gray matter of the central nervous system and consisting of the cell body of the efferent neuron and its junction (synapse) with the central process of the afferent neuron.

As a rule the afferent and efferent limbs do not connect directly in the center, one or more nerve cells being interposed between the two. These are spoken of as *connector*, *internuncial*, or *intercalated neurons* (fig. 325). The stretch reflex (p. 322) as shown by Lloyd is carried out through

a reflex arc of only two neurons, but the majority of the spinal reflex arcs in higher animals consist of several neurons, and in most reflexes each afferent neuron makes connection through collateral branches and internuncial neurons with a large number of motoneurons (fig. 326).

Injury, leading to loss of function of any one part of the reflex arc, is sufficient to destroy the function of the whole.

THE RECEPTOR ORGANS

The afferent fibers end peripherally either as bare unmyelinated filaments or in accessory structures called *receptors* (fig. 327). These are highly specialized to respond most effectively to one or other type of stimulus. When stimulated appropriately an impulse or a series of impulses is sent along the afferent fiber. Receptors are situated in the skin, muscles, tendons, etc., and in such special organs as those of sight, hearing, smell and taste. They are also contained in the walls of the respiratory and digestive tracts, mesentery, carotid sinus and other internal structures. Through receptors in these various situations information is continually being transmitted over somatic and autonomic pathways to the central nervous system. Those receptors which respond to stimuli arising in the outer world, e.g., those of the skin, eye, ear, etc., are called *exteroceptors*. Of these, those which make perception at a distance possible, i.e., those situated in the visual, auditory or olfactory sense organs, are sometimes referred to as *distance receptors* (telereceptors). Receptors lying in the mucous linings of the respiratory or digestive tracts and which, though not in immediate contact with the outer world, respond to stimuli ultimately derived therefrom are spoken of as *interoceptors*. *Proprioceptors* are those which respond to stimuli originating within the body itself, e.g., in the skeletal muscles, (p. 805) tendons, joints, heart, carotid sinus, gastro-intestinal wall, etc. Though each variety of receptor responds most readily to one particular type of stimulus—*adequate stimulus*—many will respond in some degree to stimuli of other types. The retina, for instance, can be stimulated mechanically or electrically and the receptors of taste,

though responding most effectively to chemical stimuli, may also be stimulated by an electric

them adequately is sometimes used to designate different varieties of reception organ. Thus *tango-* (touch), *chemo-* (taste, smell and the receptors of the carotid and aortic bodies) and *photo-* (sight) *receptors* are spoken of.

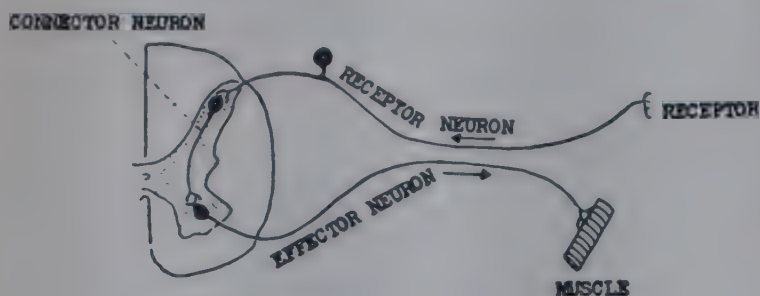


FIG. 325. Diagram of a simple reflex arc.

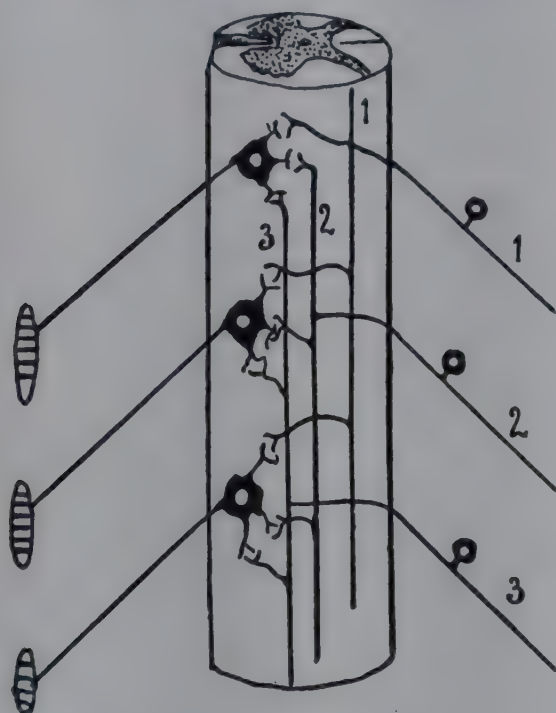


FIG. 326. Showing how an afferent nerve fiber upon entering the cord makes connections with several motor neurons, and how each of the latter is in communication with several afferent fibers. Connector neurons are not shown.

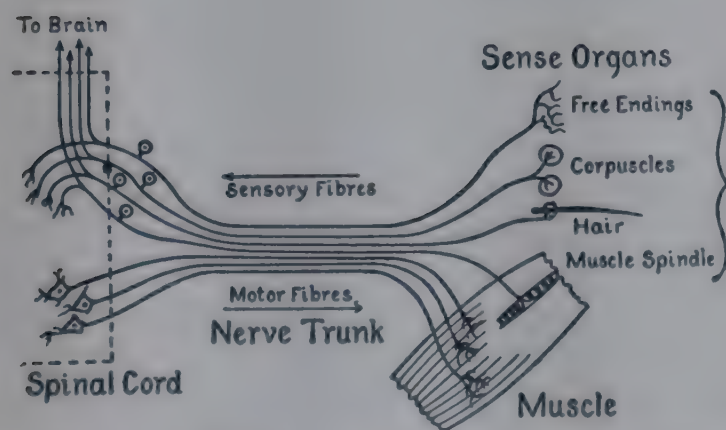


FIG. 327. Diagram to show the nervous connections between the central nervous system and the periphery (muscle and cutaneous receptors) (from Adrian, *The Basis of Sensation*).

shock applied to the tongue. A terminology based upon the type of stimulus which excites

CUTANEOUS SENSATIONS

The sensations which may be aroused by stimulation of the skin are *touch*, *cold*, *warmth* and *pain*. Each of these sensations, except the last,

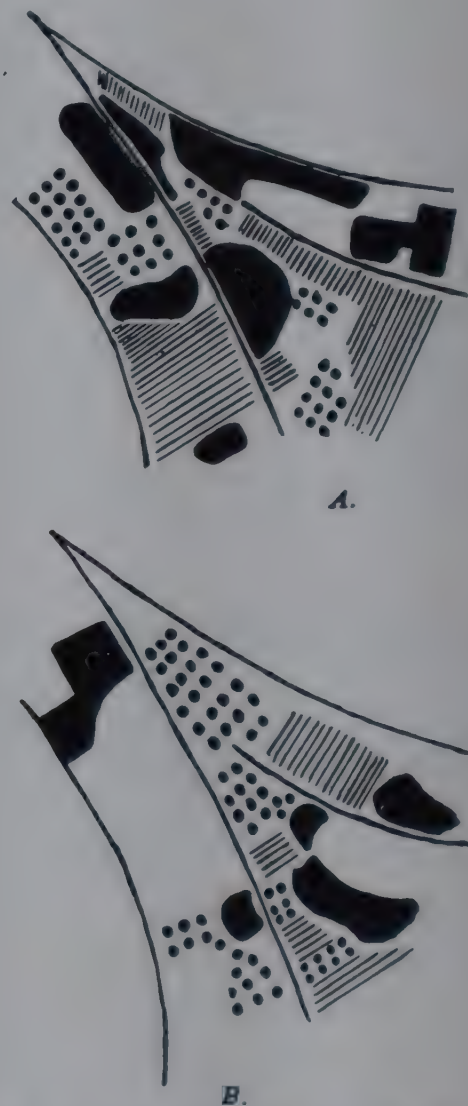


FIG. 328. Showing cold spots (A) and hot spots (B) within an area on the palm of the hand. The sensation in each case was most intense in the black areas, less intense in the lined and mildest in the dotted areas. In the blank portions no definite sensation was aroused (after Goldscheider).

mediated by a receptor or sense organ possessing distinctive structural features.

The presence of discrete endings subserving the several cutaneous sensations enables small areas to be mapped out upon the skin which are specific for one or other sensation. The areas are called touch, cold, heat or pain "spots" respectively in accordance with the sensation which their stimulation arouses (fig. 328).

If the *afferent nerve* fiber supplying one or other

receptor organ is excited *directly* by the application of the type of stimulus, e.g., touch, heat, etc., for which the receptor is adapted to respond, the characteristic sensation is not, as a rule, aroused; a painful sensation usually results.¹ Moreover, reflexes can usually be elicited much more readily by stimulating the receptors than by applying the stimulus directly to the afferent nerve, and certain reflexes cannot be evoked at all by direct excitation of the nerve fiber. Pressure upon the pad of the hind foot of the "spinal dog," for example, causes a strong extension of the whole limb—the *extensor thrust*—whereas no form of stimulus applied directly to the afferent nerve itself will produce this reflex (Sherrington). The afferent fiber before terminating in the receptor organ or as a free nerve filament loses its myelin sheath and neurilemma and appears as a naked axon (p. 777).

LIGHT TOUCH. Tactile sensation—the sensation aroused by light contact—is subserved by three types of receptor, *Meissner's corpuscles*, *Merkel's disks* and a basket-like arrangement of nerve fibers, surrounding the base of a hair follicle (Fig. 329). Meissner's corpuscles are situated in the papillae of the skin, just beneath the epidermis. They are unevenly distributed, being sparsely scattered over such a region as the volar aspect of the forearm but numerous in the skin of the hand, foot, nipple and lips, and in the mucous membrane of the tip of the tongue. They are well organized structures, consisting of irregularly coiled nerve endings with capsules of connective tissue. *Merkel's disks* consist of groups of three or more cup-shaped disks with a reticulated appearance. The nerve fiber upon approaching a group of such structures breaks up into branches, one going to each disk. Merkel's disks are found in the skin of the snouts of pigs and other mammals and in the finger-tips, lips, mouth and glans penis of man. The basket-like arrangement, surrounding the base of a hair follicle consists of a number of short, vertical, nerve filaments which end in small bulbous expansions. They are stimulated by any slight movements of the hairs.

Inequality of pressure with consequent deforma-

tion of the skin surface is the essential factor in the stimulation of touch receptors.

The sensation of light touch is tested by bringing a wisp of absorbent cotton in contact with the skin, or by the use of von Frey's esthesiometers. These consist of a series of hairs of graded thickness attached at right angles to wooden holders. The pressure in grams required to bend each hair is known. In order, therefore, to express the sensitivity of the skin to touch in terms of pressure the hair is found by trial which, when pressed vertically upon the skin until bending occurs,

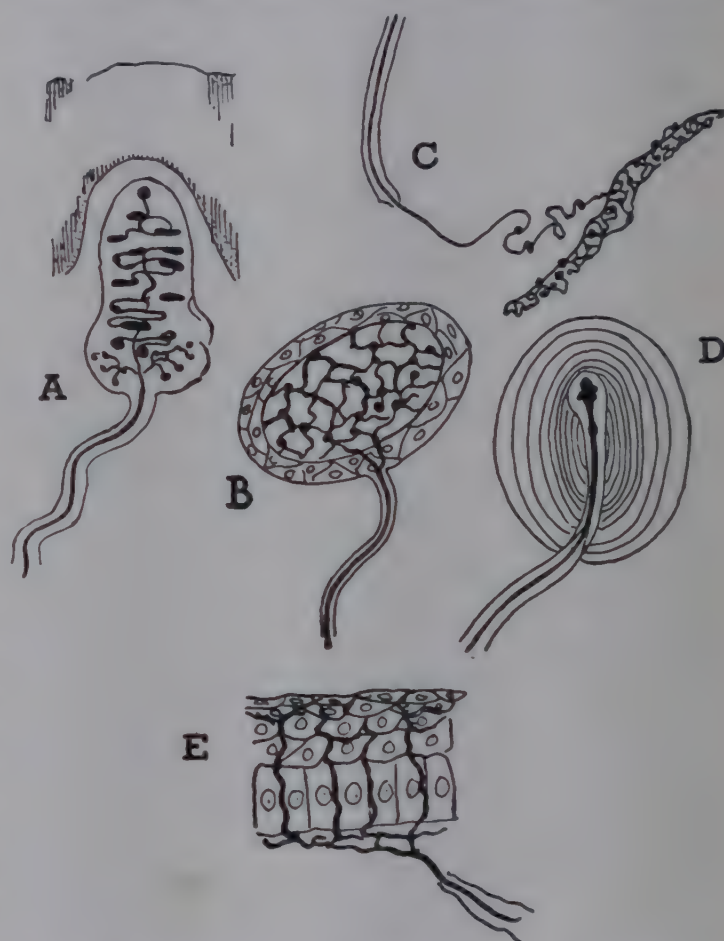


FIG. 329. Cutaneous receptors. A, Meissner's corpuscle (touch); B, Krause's end bulb (cold); C, Ruffini's end organs (warmth); D, Pacinian corpuscle (deep pressure); E, bare nerve endings in cornea (pain) (in part from Bainbridge and Menzie, *Essentials of Physiology*, Longmanns, Green and Co.).

causes the sensation. The sensitivity of the skin to touch varies widely in different regions. The minimal pressures required are given in table 74. When hairy parts, such as the back of the hand, are lightly brushed with a tuft of cotton wool the hairs serving as levers deform the skin, and thus cause stimulation of touch receptors situated in the neighborhood of the hair follicles. Shaving the hairs over such parts greatly reduces the sensitivity to touch. Other regions quite devoid of hairs such as the finger tips and lips, on the other hand, possess the highest degree of tactile sensibility.

¹ Heinbecker, Bishop and O'Leary have reported that tactile as well as painful sensations may be aroused by the electrical stimulation of the nerve trunk. The experiments were carried out upon the exposed nerves of human subjects. Stimuli of low intensity applied to the nerve aroused the sensation of touch, those of greater intensity a sensation of pain. No other type of sensation was experienced by the subjects.

TACTILE LOCALIZATION. When a tactile stimulus is applied to a point upon the skin the normal subject is capable of recognizing the location of the stimulus with a high degree of accuracy. Localization is much more precise over some regions, such as lips and tips of the fingers, than over others, such as the forearm or thigh. In certain nervous diseases this localization is grossly impaired. In lesions of the cerebral cortex the subject usually, according to Horsley, when asked to locate the stimulus indicates a point some distance upon its *proximal* side. In some diseases, notably hysteria, the subject feels the stimulus at a corresponding point on the opposite side of the body; this phenomenon is called *allocheiria*.

TABLE 74

The minimal pressures required for the elicitation of the sensation of touch from various cutaneous regions
(After Meyers)

REGION	GRAMS PER SQUARE MILLIMETER
Nose.....	2
Lips.....	2.5
Tip of finger.....	3
Back of finger.....	5
Upper arm, inner surface of thigh.....	7
Back of hand.....	12
Calf, shoulder.....	16
Abdomen.....	26
Front of leg, sole of foot.....	28
Back of forearm.....	33
Loin.....	48

The localization of a cold, hot or painful sensation is very inaccurate unless the stimulating agent actually touches the skin. Thus, heat radiated from a small object about 1 millimeter from the cutaneous surface gives rise to a diffuse sensation. The more accurate localization when contact is made with the skin is evident though the subject experiences no sensation of touch. It is likely, nevertheless, that the tactile receptors are excited, that the failure to appreciate the sensation is due to masking by the stronger stimulus, and that impulses arising in the touch endings are responsible in some manner for the more accurate localization of the other types of stimulus when these are applied directly to the skin.

TACTILE DISCRIMINATION (COMPASS TEST). If two stimuli are applied simultaneously, two distinct sensations are felt, provided the distance between the two stimulated points is sufficiently

great. Thus, when the points of a pair of compasses are blunted or covered with cotton wool and applied to the finger tip, the subject recognizes the duality of the stimulus if the points are more than about 2.3 mm. apart. When they are separated by a shorter distance a single sensation is experienced. The minimal distance at which the recognition of two stimuli is possible varies in different regions, as shown in table 75.

In the case of the limbs the power of discrimination diminishes progressively from the distal to the more proximal segments, and hairless regions in general have a higher discriminating ability than those covered with hair.

A correspondence is also exhibited between the mobility of a part and its discriminating ability. For example, the minimal distance necessary for

TABLE 75

Different cutaneous areas compared with regard to the minimal distance which must separate two stimulated points in order to arouse a double sensation
(After Meyers)

REGION	MINIMAL DISTANCE
	mm.
Volar surface of finger tip.....	2.3
Dorsal surface of third phalanx.....	6.8
Palm of hand.....	11.3
Sole of foot.....	16.0
Back of hand.....	31.6
Back of neck.....	54.0
Middle of back, upper arm and thigh.....	67.1

two stimuli to give rise to a double sensation is less for the fingers and hand than for the arm, shoulder and back, and diminishes progressively over the skin of the face from the region of the ear to the lips.

It should be pointed out that the values given in the foregoing table do not represent the distances separating individual touch receptors. For example, when single stimuli are applied *successively* to different points of the skin of the finger tip the spots from which tactile sensation can be evoked are found to be about 0.1 mm. apart. That is, when compass points are applied to the finger tip and are recognized as two stimuli several (15 to 20) touch spots are included within the intervening space.

TICKLING AND ITCHING. There has been much discussion concerning the origins of these sensations. The tickling sensation appears to be due

to the summed effects of stimulating both touch and pain endings. Section of the spinothalamic tract (which conveys pain impulses) results in the loss of the appreciation of pain but retention of the sense of touch; a tickling sensation cannot be aroused over the analgesic skin. On the other hand, the sense of touch is lost while that of pain is retained, when the skin is rendered moderately ischemic; again, the tickling sensation cannot be elicited. The *itchiness* which is experienced in the region adjacent to a slight injury, or during the healing of a more severe injury when the skin is rubbed, has the same nervous origin, being dependent upon impulses travelling by both tactile and pain fibers, but the *spontaneous* itching which is felt under the same circumstances, appears to be due to the mild stimulation of pain endings alone; more intense stimulation of the same character causes pain. This type of itchiness is affected relatively little by ischemia. Both types of itching are alike in that they are due to a chemical substance acting upon nerve endings and liberated by the damaged cells of the skin. This substance appears to be the same as that which causes the triple response. An extract of skin showing this response when injected into normal skin induces both types of itching. Histamine introduced into the skin has a similar effect. Rothman believes that itching is identical in quality with protopathic pain and is mediated by the C group of nerve fibers.

COLD is mediated by the end organs of Krause (fig. 329 B) and *warmth* probably by the end organs of Ruffini (fig. 329 C).³ Mechanical or electrical stimulation, as well as the application

³ Waterston questions the existence of definite heat and cold spots since he finds that the points from which these sensations can be aroused change from time to time in number as well as in pattern. He states that when the skin is hyperemic the entire surface responds to warmth (punctate distribution being abolished) and he believes that the entire skin surface is potentially sensitive to this sensation, the apparent punctate distribution being due simply to fluctuations in the activity of different areas. The variability in sensation, he suggests, may possibly be related to a corresponding fluctuation in the capillary circulation. The observations of Bazett and associates indicate that the diffuse nature of the temperature sensations on hyperemic skin can be best explained upon the basis of a more ready conduction of heat through the blood stream to neighboring end organs; thus, when the cutaneous blood flow is profuse heat applied to a non-sensitive point in the skin would be conducted rapidly to adjacent warm spots. The observations of Bazett and his colleagues upon the sensitivity of the prepuce support the conception of heat and cold spots and the existence of discrete receptor organs for these sensations as well as for touch (Arch. Neur. Psych. 1932, 27, 189). Waterston's view has not received general acceptance.

of heat itself, will stimulate the latter end organs and give rise to the sensation of warmth. Cold and touch spots are much less numerous than touch and pain spots.

PRESSURE upon the skin considerably greater in degree than that which elicits the sensation of touch stimulates the more deeply lying receptors known as the *Pacinian corpuscles* (fig. 329 D). The sensation of pressure is not, however, a true cutaneous sensation; the Pacinian corpuscles lie in the subcutaneous tissues or inner layers of the dermis as well as in tendons, periosteum and other deep-seated structures; their nerve fibers run chiefly, not in the cutaneous nerves, but in the sensory nerves supplying tendons and blood vessels (see p. 805).

PAIN is subserved by naked nerve endings, there being no organized end organ for this sensation. The pain nerves of the skin are described by Woolard as consisting of non-medullated fibers which terminate in the superficial layers of the dermis in delicate loops lying parallel to the skin surface, or as long naked neurofibrillae. Only occasionally do fibrils penetrate the epidermis. Bare nerve endings mediating pain are also present in the cornea (fig. 329 E) and in serous surfaces (peritoneum, pleura, etc.); touch, cold and warm endings are absent and the corresponding sensations cannot be aroused from these locations. Although it is a general belief that the cornea contains only pain endings and that any stimulus, if intense enough to evoke a response at all, causes pain, it is claimed by some that the sensation of touch without pain can be aroused by a very mild stimulus such as a jet of isotonic saline.

The pain endings do not respond selectively to one variety of stimulus but to any type whether mechanical, chemical or thermal, provided it is sufficiently intense. The pain stimulus, whatever it may be, has one property in common, namely, that it causes or threatens injury. The sensation of pain therefore serves a protective purpose, giving warning of the injurious nature of a stimulus rather than information as to any more specific quality. Stimuli which arouse painful sensations also provoke reflex actions which have the following features. (a) They comprise movements for *protection* or *defense* or for the withdrawal of the part from the noxious agent. (b) They are *prepotent*, other less urgent reflexes being for the time inhibited. (c) They are *imperative*. Such reflexes are called *nociceptive*.

Whereas, the touch spots are more numerous toward the peripheral parts of the body, the pain

spots are more profuse near the roots of the limbs. Thus, in the axillae, supraclavicular fossae and inguinal regions, their number is around 200 per sq. cm., but there are no more than from 40 to 70 per sq. cm. over the palms and soles, the tip of the nose and the ear.

It used to be thought that the production of pain was not a function of any one type of nerve ending, but that any skin receptor if stimulated with sufficient intensity would give rise to the sensation. This conception has been refuted by modern work which indicates that the various types of cutaneous receptors are specific in function (see p. 808).

The nature of cutaneous pain. Pain in the skin, although usually described as of several different kinds, e.g., burning, pricking, cutting etc., is always, according to Lewis, of the same quality, the apparent differences being due solely to variations in the duration of the sensation. A blind-fold subject, for example, is unable to distinguish between the pain caused by a pin prick, a hot point, a punctate electrical stimulus or the plucking of a hair, provided no associated non-painful sensation gives the patient a clue as to the nature of the stimulating agent. These pains would all be described as sharp, "bright" or pricking. A burning pain is experienced when the sensation is more prolonged, whether caused by heat or ultra-violet light or by a chemical or mechanical irritant.

It is a common experience that a single painful stimulus applied to the skin, if intense enough, may give rise to two sensations separated by a short interval. The first pain is short and sharp, the second, more prolonged and severe. The observations of Lewis and Pochin upon this phenomenon indicate that pain impulses are conveyed from the skin by two sets of nerve fibers, one of which is rapidly conducting, the other with a much slower conduction rate. They found that ischemia of the skin of the arm, induced by arresting the circulation, abolished the first response to the needle prick, the second response being unaltered for a time but later became reduced. Cocaine, on the other hand, abolished the second response before the first. It was shown moreover, that the time interval between the two responses was prolonged as the length of the nerve between the point of stimulation and the central nervous system was increased, a fact which seems to demonstrate decisively the existence of a fast and a slow pathway for the transmission of cutaneous pain. The time interval between the two responses is 1.9

sec. when the stimulus is applied to the toe, 1.3 sec. to the knee and only 0.9 sec. to the upper limit of the thigh.

The first painful sensation of the dual response appears to travel by the fibers of rapid conduction belonging to Erlanger's and Gasser's B group (p. 790), for they are more susceptible to asphyxia, whereas, the second pain response is transmitted by the slowly conducting C group of fibers, since they are more readily affected by cocaine.

A third type of pain response follows some little time after certain forms of injury, e.g., scorching, scalding, sun-burn or the application of an irritating agent, and persists for a variable period. Even a slight burn may cause a dull pain which continues for many minutes. This pain evidently is caused by the release of a chemical substance from the damaged tissues and not by direct action of the stimulating agent upon the nerve terminals. Arresting the blood supply to the part intensifies and prolongs the pain. The nature of the chemical excitant is unknown, but it is not H substance (p. 269), potassium, nor acetylcholine; nor is it due to altered pH.

Deep pain. Pain can be provoked by the appropriate stimulation of muscle, bone and periosteum, joints, tendon and fascia, and arteries, and of the thoracic or abdominal viscera. Visceral and referred pain are dealt with in Chapter XLV.

Muscles, tendons and fasciae are especially susceptible to painful stimulation by chemical agents. The injection of a few drops of a 6 per cent saline solution into one of these structures causes pain. Muscle is relatively insensitive to pricking or cutting but pain is aroused by pressure, e.g., pinching or squeezing, or by exercising under ischemic conditions (p. 257). Tension acts also as a pain stimulus for muscle, tendon or fascia. Deep pain is diffuse, usually continuous and poorly localized. Pain occurring in ischemic muscle during activity is due to a chemical irritant produced by the active tissues and which accumulates and stimulates the pain endings when the circulation to the part is arrested or considerably reduced. This substance is referred to as factor P by Lewis and his associates. The soreness of healthy muscles which comes on some hours after exercise is of the same nature.

Periosteum and cancellous bone are very sensitive to the various types of mechanical stimulation, but compact bone is insensitive to drilling or sawing. The arteries give rise to painful sensations when pricked, but the walls of the veins are insensitive

Deep pain differs in certain particulars from superficial pain in that it is not associated with protective reflexes and when severe, is accompanied by sweating, nausea, slowing of the pulse and a fall in blood pressure. The pain is best described as "sickening". Cutaneous pain cannot be appropriately described in this way and it is accompanied by quickening rather than slowing of the pulse, and a rise in blood pressure.

Hyperalgesia and the nocifensor nerves. In many persons an area of tenderness develops around even a small cutaneous injury and spreads over a considerable distance in all directions. The soreness starts within a few seconds, increases to a maximum in from 15 to 30 minutes and lasts for hours or, with a more severe injury, for days. The threshold for pain as tested by a needle prick is lowered only slightly over the area, but the pain when aroused is diffuse, and unusually intense and prolonged. This phenomenon has been studied by Lewis and his associates. Injury was produced by prolonged faradic stimulation of the skin, by crushing a small cutaneous fold with forceps or by direct stimulation of a cutaneous nerve trunk or one of its branches. A similar area of cutaneous hyperalgesia may result from an injury or an inflammatory process involving deep-lying tissue or mucous membrane. Thus, stimulation of a dental nerve or of the mucous membrane of the maxillary antrum is followed by tenderness of the overlying skin of the cheek. Lewis' experiments point to a specific system of nerves in the skin as being responsible for the hyperalgesia. They are believed to be quite distinct from the pain fibers which are stimulated directly by the injurious agent and through which pain sensations are ordinarily registered. This system, which is referred to as the *nocifensor nerves* is pictured as finely branching and rich end-plexus within the skin; it leads into more deeply lying axons which, in turn, run into subcutaneous nerve trunks. The action of this system of nerves serves to ward off further injury and to put the injured part at rest, hence their name. They are not sympathetic filaments, for the phenomenon is observed in skin completely deprived of its sympathetic innervation. Lewis bases his conclusion that the nerves which respond in the ordinary way to pain stimuli are not responsible, upon the diffuse and poorly localized character of the hyperalgesia, and upon the effects of ischemia and of cocaine. The nerve fibers responsible for the hyperalgesia are paralysed by ischemia but are little effected by cocaine. Pain sensations, on the contrary, are affected rela-

tively little by ischemia but are readily abolished by cocaine. He rejects the idea that substances produced at the injured site and diffused through the skin are the cause of the soreness because, if a *small* area is anesthetized with cocaine and an injury produced within it, hyperalgesia does not develop in the surrounding part until after the effect of the anesthetic has passed off.

Dissociation of sensations. In disease, the several modalities of sensation, touch, cold, warmth, and pain may be lost separately; or they may be temporarily dissociated by artificial means as by asphyxia, cocaine or the application of cold. Thus, the cutaneous sensations, touch, cold, warmth and pain are lost in this order when the skin is made ischemic. If it is cocaineized, the appreciation of cold is lost first then follow in order the senses of warmth, pain and touch. Cooling the skin causes first, failure in the response of the cold receptors, then in succession the sensations of touch, pain and warmth are lost. Also, after section of a cutaneous nerve, the area of pain loss is smaller than that of touch, there is thus a boundary zone from which a response to a painful stimulus, such as that of a pin prick, can be obtained but which is insensitive to light touch.

Epicritic, protopathic and deep sensibilities

Head and his associates, from the study of a large number of peripheral nerve injuries, grouped the several sensations into three classes: (1) *epicritic*, (2) *protopathic* and (3) *deep sensibility*. Under *epicritic sensibility* are included light touch over hairless parts, the power of localizing the point touched, the detection of two individual sensations when two points are touched simultaneously, and the appreciation of finer grades of temperature, cool and warm, i.e., temperatures ranging between about 40° and 25°C. *Protopathic sensibility* is a more primitive type of sensation and more widely distributed. It includes pain and the temperature sensations aroused by extremes of heat and cold—above 40° to 50°C. and below 20° to 25°C. In other words, protopathic sensibility possesses a high threshold; but, through the stimulus must be strong in order to arouse a sensation, this once aroused is intense, diffuse, poorly localized and peculiarly unpleasant in quality. These latter qualities of protopathic sensibility are particularly prominent in the absence of epicritic sensibility, which therefore has been considered to exert a restraining influence upon the former. The glans penis possesses only protopathic and deep sensibilities. *Deep sensi-*

bility is aroused by the stimulation of structures in the deeper layers of the skin, and in the muscles, bones and joints. The sensations aroused are, as a rule, well localized; they consist of *pain*, *pressure* and the sense of *position* or *movement* of a part (see also under proprioceptors).

For the purpose of studying these three sensations Head underwent an operation in which his radial nerve and the cutaneous branches of the musculo-cutaneous nerve were severed at the elbow. After the operation there was *complete* loss of cutaneous sensation over the radial half of the back of the hand. Surrounding this was a narrow zone in which epicritic sensibility alone was lost; protopathic was retained. This is due to overlapping of the protopathic innervation of the adjacent unaffected skin area. Over a small triangular area of skin at the wrist the relationship between these two sensations was reversed; protopathic sensibility was lost but epicritic retained. Stopford has since shown that this latter type of dissociation of the two groups of sensations is also characteristic of section of a posterior root—the area of protopathic loss being much greater than epicritic. In Head's experiment evidence of returning sensation (due to regeneration of the nerves) was noticed on the 43rd day after operation when the zone of protopathic sensation was found to have become broader and to have encroached upon the totally insensitive area. The original area insensitive to light touch remained unreduced. Within about six months *protopathic* sensibility had returned over nearly the entire area, yet the extent of the *epicritic* loss remained unaltered. The first signs of the return of epicritic sensation was not observed until a year after the operation and was not complete after the lapse of two years.

Deep sensibility is evidently not mediated by fibers in cutaneous nerves, but by afferent fibers running with the motor branches, for this sensation remained unaffected by the operation. Light pressure could be everywhere appreciated. This is an important point to remember in the investigation of nerve lesions since it shows that crude methods for studying the sensations of touch may fail to reveal any loss. The superficial touch receptors are stimulated alone by light contact with a wisp of cotton or by the pressure of a fine hair, whereas a pressure not very much greater, as with the point of a pencil, will stimulate the deeper lying pressure receptors (Pacinian corpuscles) whose nerve fibers may be intact while those of true touch are destroyed. As a result of these experiments in which dissociation of the three types of sensation were clearly demonstrated Head and his associates concluded that each sensation was mediated by a separate and structurally distinct group of fibers. Unquestionably, a deep sensibility is conveyed by fibers separate from those responsible for cutaneous sensations, but that epicritic and protopathic sensations has each its specific fiber group has been seriously questioned. The work of Erlanger and Gasser and of Ranson appeared to lend support to Head's interpretation. The C fibers of the former

authors were suggested as the possible mediators of protopathic sensation and the A group, of epicritic. Ranson had previously described unmyelinated fibers in the cutaneous nerves which, since they were believed to mediate pain might offer an anatomical basis for the primitive protopathic sensations. The existence of protopathic sensation only in the glans penis and the dissociation of the two sensations, which as shown by Stopford result from section of the posterior roots, also supported Head's conception of two distinct sets of fibers. Experiments by other neurologists, on the other hand, have failed to substantiate this contention (see Trotter and Davies). Some would explain the two classes of cutaneous sensation following nerve section upon the basis of different rates of regeneration of the receptor organs, the terminals of the pain fibers being thought to regenerate first. Fine discrimination, according to Heinbecker, is dependent upon the *number* of active end organs within a given area. The zone of protopathic sensibility surrounding an anesthetic area caused by nerve section is ascribed simply to the presence, in reduced numbers, of intact afferent endings which have overlapped the field of distribution of the sectioned fibers. The recognition of these two types of sensation, whatever may be their anatomical basis, is, however, of distinct value from a clinical standpoint.

Vibration sense. This is the ability to perceive stimuli of a vibratory nature applied to the skin by means of a tuning-fork or other rapidly oscillating instrument. There is some doubt as to the character and situation of the receptors upon which this sense depends. According to some investigators they are present in bone, periosteum and tendons, and are therefore part of the system of deep sensibility; others contend that they are confined to the skin. Pollock has shown that the vibration sense is retained though the superficial sensations (epicritic and protopathic) have been lost, which indicates that it is conveyed by fibers other than those mediating the latter sensations, namely by the deep system. The receptors are probably situated in the subcutaneous tissues or though less likely in the deeper layers of the skin; they are fewer in bone and periosteum. The receptors sensitive to pressure, namely, the Pacinian corpuscles, may be those concerned with the registration of vibratory sensations. Others claim to have obtained evidence indicating that the stretch receptors in neighboring muscles respond to the stimulus of vibration.

THE PROPRIOCEPTORS OF MUSCLES, TENDONS AND JOINTS

The receptors situated in skeletal muscles and in the tendons and joints furnish information to the central nervous system concerning the move-

ments and positions of the limbs and other parts. Afferent fibers carrying this information make up from $\frac{1}{4}$ to $\frac{1}{2}$ of the fibers in a so-called motor nerve. As a result of the messages received by the nervous system, the contractions of individual muscles and groups of muscles are coördinated to produce smooth, finely adjusted and effective movements which would be impossible in the absence of such guidance from the periphery. For this reason the term *kinesthetic* is applied to this group of receptors. A proportion of these afferent impulses arouse no sensation, their information being delivered to centers lying beneath consciousness. To others are due the sensations grouped in the last section under deep sensibility. The receptors in the situations mentioned respond to mechanical stimulation, e.g., pressure or stretch. These types of stimulus are furnished by the strains and stresses set up in the muscles, tendons and joints during muscular contraction.

The sensory endings in the various situations mentioned above are of four main types: (1) *muscle spindles*, (2) *Golgi corpuscles*, (3) *Pacinian corpuscles*, and (4) *free nerve endings*.

(1) *The muscle spindle* is a fusiform body from .75 to 4 mm. long and from 0.1 to 0.2 mm. broad lying parallel to and between the muscle fibers (fig. 330). It is constituted of a bundle of from 2 to 10 muscle fibers (intrafusal fibers) enclosed in a fibrous capsule. The latter is separated from the intrafusal fibers by a lymph space bridged across by delicate septa. The intrafusal fibers differ from the ordinary fibers of the muscle in being smaller and more circular on cross section, and in having a greater number of nuclei and coarser striations. The nerve supply of the spindle is double—afferent and efferent. The afferent enters the spindle about its center, the latter more toward one or other end. The efferent fibers are distributed to end organs in the intrafusal fiber which resemble but are not identical in structure with the motor end plates of ordinary muscle fibers. Upon entering the spindle and losing its myelin sheath and neurilemma, an afferent fiber may end in one or other of two ways. (a) Some become flat and ribbon-like and wind themselves in rings or spirals (*annulo-spiral endings*) about the intrafusal fibers. (b) Others ramify upon the latter's surface in a manner suggesting a spray of flowers ("*flower spray*" ending of Ruffini).

(2) *The Golgi corpuscles* (fig. 330) are situated in tendons and consist of a bundle of tendinous fibers surrounded by a lymph space and enclosed within a fibrous capsule. Afferent nerve fibers

enter the organ near its center and ramify upon its constituent fibers. Tension is the adequate stimulus for these receptors.

(3) *The Pacinian corpuscles* are oval bodies composed of concentric laminae, like the "skins" of a sectioned onion. The afferent fiber penetrates to the center of the corpuscle. Pressure with elongation of the organ and consequent stretching of the nerve ending is the adequate stimulus. These receptor organs are found in tendons, joints, periosteum, especially beneath tendinous insertions, in fasciae covering muscles and in subcutaneous tissues (fig. 329). They are also found in the mesentery. The structure of these receptors appears to be such that a mechanical stimulus such as stretching, pressure, etc., induced by muscular action will be applied most effectively to the naked axis cylinder within its center.

(4) *Bare nerve endings* lie between the muscle fibers, in tendons and in the fasciae and joints. They mediate deep pain.

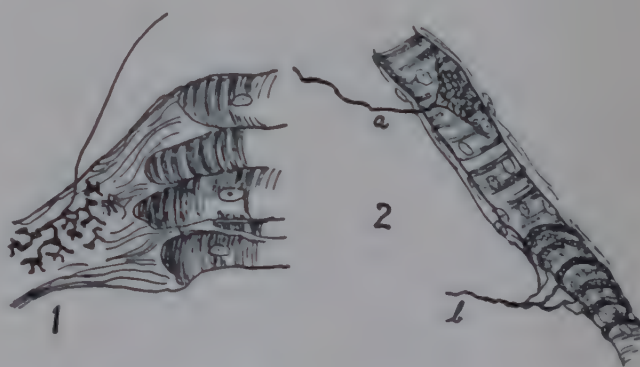


FIG. 330. 1. Golgi ending in tendon; 2. intrafusal fiber showing, a, muscle flower spray and b. annulo-spiral endings.

THE RESPONSES OF CERTAIN SKIN AND MUSCLE RECEPTORS

When non-polarizable electrodes are placed upon a mixed nerve of an intact animal at rest or upon a posterior root, a continuous stream of action currents can be recorded. These impulses of the "resting" nerve have a relatively low frequency—from 3 to 5 per second. They arise mainly from proprioceptors of muscle and tendons. The mere passive movement of the limb supplied by fibers entering the posterior root under investigation causes a prompt and pronounced rise in the impulse frequency. Light pressure upon the skin or even brushing the hairs also causes a rise in frequency as the result of stimulation of skin receptors. Adrian and his associates have recorded the afferent impulses from the frog's sciatic set up by stretching the gastrocnemius, from a nerve fiber supplying a single touch receptor of

the frog's skin, and from the plantar digital nerve of the cat during the stimulation of the receptors of pain, touch or pressure in the skin of the toe pad.

When the receptors in the skin of the toe pad of the cat were stimulated by light contact or pressure the record taken from the plantar digital nerve showed a rhythmical discharge of impulses having a frequency of 150 per second. The frequency rose with an increase in the degree of pressure. Adrian and Umrath were able to locate a single Pacinian corpuscle and stimulate it by pressure with a hair or a fine glass rod. The impulses were recorded by means of an amplifier system in conjunction with a Matthews oscillograph. Pressure upon the end organ caused a discharge of impulses at a rate as high as 100 per second. A group of corpuscles lie beneath the flexor muscle of the toe; movement of the phalangeal joint crossed by the muscle stimulated the receptors and caused a discharge of impulses. Temperature changes failed to excite. The response of a single muscle spindle to stretch was also investigated by Adrian and Zotterman. They employed the sterno-cutaneous muscle of the frog which arises from the abdominal wall and is inserted into the skin over the chest. The entire muscle contains only 3 or 4 muscle spindles, and by the successive removal of portions of the muscle a preparation containing a single spindle with its nerve fiber intact was obtained. A sudden stretch (by means of a weight) applied to the muscle caused a rhythmical discharge of impulses along the nerve. The end organ apparently obeys the all or none law since increasing the strength of the stimulus above the threshold did not increase the *magnitude* of the electrical response. The *frequency* of the responses varied, however, directly with the intensity of the stimulus from 5 to 100 per second. A higher rate than this (300 per second) was obtained from a single touch receptor of the frog's skin by Adrian, Cattell and Hoagland, a blast of air being employed as the stimulus.

Matthews employed a small extensor muscle situated upon the outer side of the middle toe of the frog. This muscle contains a single muscle spindle. The afferent impulses were recorded by means of an amplifier and oscillograph from a small branch of the peroneal nerve supplying the muscle. The muscle spindle was stimulated by loading the muscle at various rates and with weights of different amounts. It was found that: (a) the frequency of the impulses set up were roughly proportional to the logarithm of the load, (b) at 16°C. the maximum impulse frequency

obtainable was 290 per second. That is, each impulse followed its predecessor at an interval of only 0.0035 second. It follows therefore that each impulse traveled within the relative refractory period (0.01 second) of the preceding one. For this reason, some reduction (15 to 20 per cent) in the magnitude of the action potential waves occurs when they follow one another in rapid succession. Upon altering the temperature of the preparation the maximum frequency of the impulses varied in the same way as did the refractory period of nerve; that is, raising the temperature which has the effect of shortening the refractory period of nerve also shortens the interval between the impulses set up by maximal stimulation of the muscle spindle. (c) Passive stretch is an adequate stimulus to the muscle spindle provided the stretching force rises to its maximum at a sufficiently rapid rate. That the impulses recorded from the afferent nerve originated in the spindle was evidenced by the fact that when it was rendered functionless (by constricting it tightly with a thread) no impulses could be set up thereafter by stretching the muscle. It has been further shown by Matthews for mammalian muscle that though the two elements of the spindle ("flower spray" and annulo-spiral, p. 805) are stimulated by *passive* stretch, each behaves differently to *active* contraction of the muscle. The responses of the "flower spray" endings cease during contraction which apparently relieves the strain upon them. Those from the annulo-spiral endings also cease if the contraction is submaximal. With a supra-maximal contraction, however, they increase in frequency, due then, it is believed, to a contraction of the intrafusal fibers. The Golgi endings in tendon respond to stretch whether passive or induced by contraction of the muscle.

Adaptation

The rhythmical discharge of impulses set up by stimulation of a receptor gradually diminishes in frequency and may soon cease entirely, though the stimulus continues to be applied at its original intensity. If, for example, the touch receptors of the cat's toe pad are excited by resting a glass disc lightly upon the skin a burst of impulses occurs at high frequency for from $\frac{1}{10}$ to $\frac{1}{8}$ second, but have entirely ceased by the end of $\frac{1}{4}$ second. After this, pressure exerted upon the disc is followed by a second series of impulses which again comes to an end though the pressure is maintained unchanged. This phenomenon is spoken of as *adaptation* (fig. 331). The gradual numbing of sensation to a constant stimulus is a common experience. We speak of "becoming accustomed" to some or other environmental change which initially caused a very definite effect. The olfactory endings, for instance, soon become adapted to the action of most odorous substances, and a

light object placed upon the hand soon becomes imperceptible. We do not feel the contact of our clothes; the ticking of a clock after a time is not heard; and a hot bath feels much hotter when one first enters it than after a short period of immersion. The receptors of the retina also undergo rapid adaptation, failing to respond after a brief period of stimulation. For this reason a small moving object is more readily perceived than a stationary one, and when one directs his attention to a motionless object the eyeballs are kept constantly moving in order to stimulate the receptors intermittently.

Adaptation should not be confused with fatigue. It occurs to the same extent whether the frequency of discharge is slow or rapid; if it were a fatigue phenom-

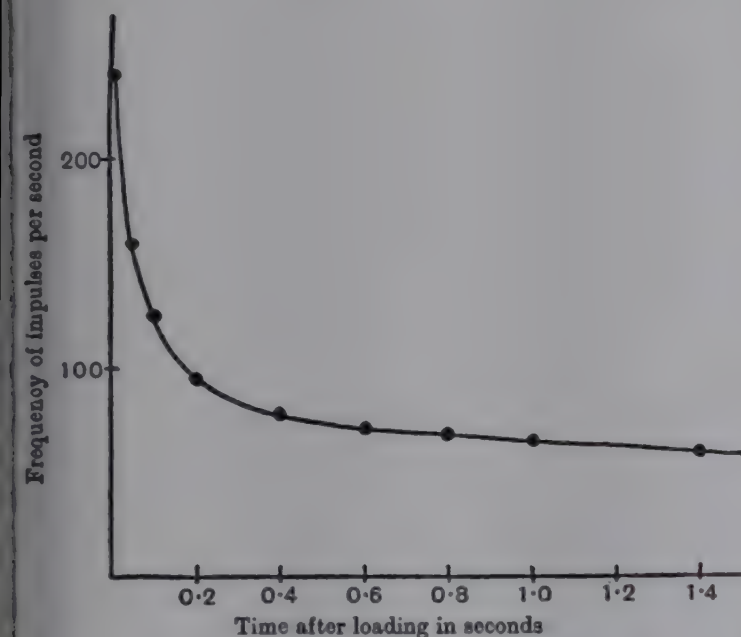


FIG. 331. Adaptation. Graph of response during first second after sudden loading with a large load. 100 gm. Temperature 14 C. (after Matthews).

enon it should of course be more evident at rapid discharge rates. Furthermore, the excitability of the adapted end organ to a fresh stimulus is not reduced, and whereas fatigue is affected by oxygen lack, adaptation is not. Adaptation is a property common to receptors whether of skin, muscle, viscera or special sense organs. Its rate of development, however, is different for the several types of end organ, being very rapid for those of touch, slower for those of pressure and warmth and still slower for those of pain and for the muscle spindle. Receptors whose function it is to record sudden changes in the external environment adapt rapidly. This is necessary in order that, having responded to a given environmental change and conveyed their message to the central nervous system, the receptors shall again be ready to respond to another stimulus, and also that information received from receptors stimulated successively shall not be confused. We are aware for instance, of the movement of a light

object over the skin since successive touch receptors respond instantly to the stimulus and adapt rapidly. If rapid adaptation did not occur, that is, if the discharge of impulses outlasted to any appreciable extent the duration of the external stimulus, the subsequent stimulation of neighboring receptors would result in a diffuse ill-defined sensation. It is necessary, on the other hand, for the muscle spindle to adapt very slowly, since upon this receptor depends in part the reflex maintenance of a continued tonic contraction of postural muscles. It would seem requisite, on the other hand, that proprioceptors giving information concerning the *movements* of muscles and joints should adapt rapidly. There is little information, however, upon this point. The proprioceptors of the carotid sinus and aorta adapt slowly, those excited by inflation of the lung also have a slow rate of adaptation. Sudden forcible inflation of the lung, for example, causes a burst of impulses at the rate of 150 per second; by the end of the first second the frequency has only fallen to 115 per second.

A comparison of receptor and nerve fiber responses

In general the nerve fiber and the end organ (or rather the nervous element of the latter) behave similarly. Both require for excitation a stimulus of a certain minimal strength and this must rise to its maximum value at a certain rate and have a certain minimal duration (p. 781). Both obey the all or none law and have absolute refractory periods of about the same duration. There are certain differences, however, between the responses of the two structures, and some of these have already been pointed out. The sense organ possesses a low threshold for one type of stimulus whereas the nerve fiber responds unselectively to various types. The later stages of recovery (relative refractory period) of the end organ are slower than those of the nerve fiber. The sense organ also differs from the nerve fiber in giving a rhythmical response to persistent stimulation. When a constant current of moderate strength is sent into a nerve a single impulse results, the refractory phase follows and though the current continues to flow a second response does not occur when the nerve recovers. If the stimulus, however, is very intense a short series of impulses may result. The apparent differences in response between the nerve fiber and end organ to persistent stimulation is therefore only quantitative. The nerve adapts rapidly, the sensory endings slowly. As a matter of fact the touch receptors adapt almost as rapidly as the nerve fiber itself (fig. 332). The rhythmical nature of the end organ response is thought to be due to the stimulus causing a

state of persistent depolarization in the surface film of the non-medullated ending within the receptor. The depolarized section of nerve then acts as a constant stimulus to the rest of the fiber. Lillie's iron wire model (p. 791), for instance, will respond rhythmically if the protective film of oxide is prevented from forming upon a terminal section of the wire. The maintenance of this part in a depolarized or active state causes a series of electrochemical reactions to be transmitted down the wire, the protective film forming upon the length of the wire after each wave has passed. Adrian also found that when the end of a nerve is injured rhythmical responses of high frequency are set up. These are probably the result of increased permeability of the damaged surface film, which therefore remains in a permanently depolarized state. These observations suggest that a mechan-

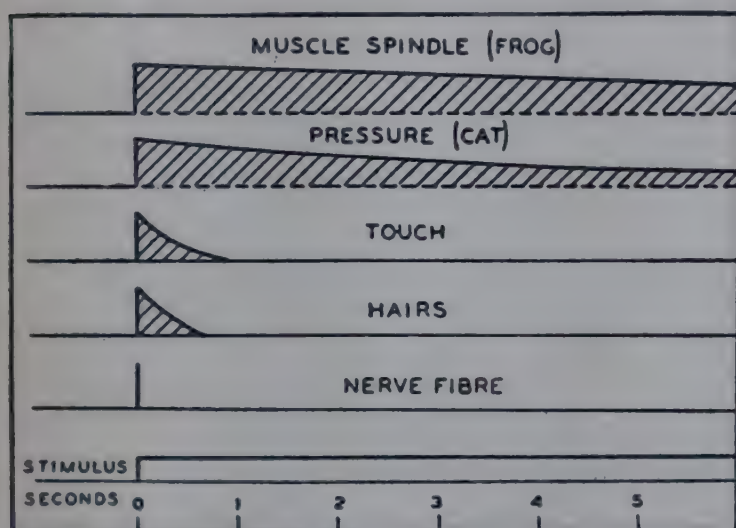


FIG. 332. Showing the response of nerve fiber and of different types of receptor to a continued stimulus. Adaptation is most rapid in the nerve fiber and slowest in the muscle spindle (from Adrian, *The Basis of Sensation*, Christophers, London).

ical stimulus applied to a sense organ causes deformation of its nerve ending with the production of analogous changes in the surface film which, persisting for a short space of time, cause the rhythmical discharge.

THE INTENSITY AND QUALITY OF SENSATION. SPECIFIC NERVE "ENERGIES"

It has already been pointed out (p. 786) that the form and magnitude of the electrical response and so presumably of the nerve impulse are not altered by increasing the intensity of the stimulus applied to a receptor organ. So far as is known the only effect of raising the intensity of the stimulus is to increase the frequency of the impulses discharged. *Intensity of sensation* is believed, therefore, to depend upon the number of impulses

reaching the sensorium per unit of time. The number of impulses reaching the sensory areas of the brain in a given time is dependent not only upon the frequency of the impulses arriving by each fiber but also upon the number of fibers involved. What may be termed the *massiveness* of the sensation is probably largely dependent upon the latter factor.

To what are due the different *qualities of sensation*? Is each type of sensation, e.g., touch, pain, sight, hearing, etc., mediated by a specific type of nerve fiber, that is, one with a distinctive type of end organ and which conveys impulses to a particular region of the brain? However stimulated does each type of end organ always produce the same quality of sensation? On the other hand, is the type of sensation dependent upon the induction in non-specific nerve endings of some change characteristic of the type of stimulus applied, the characteristic effect of the stimulus being then conveyed as a message to consciousness? The first view, which is generally accepted, is spoken of as the *doctrine of specific nerve energies*. The principle was enunciated in 1838 by Johannes Müller, though it had previously been suggested by Sir Charles Bell of Edinburgh. It was extended by Helmholtz to apply to the different qualities embraced within a single type of sensation, as in his resonance theory of hearing—the appreciation of variations in pitch being dependent, it was claimed, upon the situation in the cochlea of the particular end organs which were stimulated. Also, in Young's theory of color vision the appreciation of the different primary colors was attributed to the presence of distinct sets of fibers.

Evidence for the existence of specific nerve fibers can be derived from common experience. Mechanical stimulation of the retina, for example, causes a visual sensation only; a mechanical stimulus applied to the ear produces a sensation of sound. The presence in the skin of definite "spots" for touch, pain, pressure, etc., also points to the different cutaneous sensations being dependent upon the adequate stimulation of specific endings, each of which transmits its message to the central nervous system along a definite pathway. The stimulation of a touch spot gives rise to a feeling of touch, of a warm or cold spot to a sensation of warmth or cold, and the stimulation of a pain spot to pain. The specific nature of the touch receptors in the skin of the frog is indicated by the experiments of Adrian, Cattell and Hoagland; these receptors cannot at any rate give rise to pain,

for when they were stimulated to discharge impulses at the maximum rate (300 per second) there was no indication that the sensation was painful. A stimulus which would cause an impulse discharge of this frequency from a pain ending would certainly cause severe pain. Comparable results were obtained from the touch receptors at the roots of the hairs in the guinea pig. It has also been shown that a pressure receptor (Pacinian corpuscle) cannot give rise to pain nor is it stimulated by temperature changes.

Granted that specific fibers do exist, there is the further question,—are the messages emitted by the various end organs and transmitted along the nerve fibers identical, and do the qualities of sensation depend solely upon the connections which the respective fibers eventually make with cells in the brain? Or, on the other hand, does the specific function of the fiber depend upon some distinctive character of the impulse which it transmits? For example, do the impulses set up by stimulating a pain ending differ in some significant way from those originating in a touch receptor?

Though in general the impulses, whatever their origin or whether motor or sensory, are closely similar, certain quantitative and qualitative differences do exist. Erlanger and Gasser (p. 789), for example, showed that the axon potentials of different fibers had different conduction rates and amplitudes. Adrian and others have shown differences in the frequency of the impulses. Impulses may therefore differ from one another in (a) conduction rate, (b) magnitude or (c) frequency. Some such differences as these might possibly serve as a basis for the several qualities of sensation.

It seems unlikely that differences in frequency of the impulses can be a factor, since the impulses aroused by touch may have as high a discharge rate as those aroused by pain.³ The fibers supplying the receptors

of the skin are of smaller diameter than those going to muscle proprioceptors, which indicates that the former have slower conduction rates than the latter, and Matthews actually found that the impulses set up by stimulating a muscle spindle (which are supplied by alpha fibers of the A group, p. 790) had a higher conduction rate than those originating in a touch receptor (which are probably supplied by beta fibers of the A group). Again, the impulses set up by the application of heat to the skin have a slower conduction rate than those originating in a touch receptor, while pain impulses, in part at least, are believed to be transmitted over fibers (C group) having the slowest conduction rate of all. The form or attitude of the action potential waves recorded from one type of fiber may also show certain differences from those traveling over another type.

Nevertheless, there is little reason to believe that any of the differences mentioned—frequency, conduction rates, form or amplitude⁴—play a major rôle in determining the qualities of sensation. Qualities of sensation are determined by the particular type of end organ stimulated (which is specially adapted to respond to one type of stimulus) and are ultimately dependent on the nerve cells in the brain where the impulses arrive. As someone has expressed it, if impulses arising in the retina were directed to the temporal lobe and auditory impulses to the occipital lobe we should hear the lightning and see the thunder. The characters of the messages themselves, e.g., their conduction rates or amplitude, may however and probably do play their part in aiding the central nervous system to sort out the impulses from various sources and direct them to their destinations. Within the central nervous system each afferent fiber makes connections with several nerve cells. Thus several alternate pathways exist, and the slight differences in the characters of the impulses may be factors determining the course which shall be taken.

³ The impulses in the optic nerve during retinal stimulation have about the same frequency as those from a cutaneous receptor.

⁴ Another conceivable possibility is that impulses from different receptors might show characteristic groupings which might serve as a basis for sensation, but there is no evidence that such occurs.

CHAPTER LXV

REFLEX ACTION

The point of contact through which physiological continuity is established between two neurons is called the *synapse*. The axon of the neuron divide into numerous filaments which terminate in small button-like expansions known as end-feet (*pieds* or *boutons terminaux*) which are applied to the surface of the body or dendrites of another neuron (fig. 333). A single anterior horn cell shows several hundred (up to 1300) such contacts. It is generally taught that no structural continuity exists between neurons, but merely contact in the manner described. The fact that when a neuron is injured Wallerian degeneration (p. 779) does not extend beyond its boundaries to involve a neighboring neuron supports this conclusion. The end feet themselves quickly show degenerative changes after the axon has been interrupted; within from 24 to 72 hours they become swollen and at the end of about 120 hours undergo granulation and disintegration. The absence of protoplasmic continuity between two neurons implies that something in the nature of a surface film, though this be no more than a single molecular layer, is interposed. Such a film will provide a site for the development of surface phenomena, e.g., the formation of an electric double layer upon which the peculiar properties of the synapse probably depend. The synapse might therefore constitute a point of raised resistance—a higher threshold than that of the nerve fiber itself—which the impulse would need to cross or “step over” in order to reach another neuron. Or the synapse might provide a mechanism through which a *fresh* impulse is set up, rather than that it simply interposed new conditions in the path of the original one.

THE CHARACTERISTIC FEATURES OF REFLEX ACTION

Spinal reflex action shows several phenomena which have been studied intensively by Sherrington and his associates and have been generally considered to indicate a basic difference between conduction over reflex arcs and conduction in the nerve fiber. These special features, which will be described in this chapter, have been attributed to the synapse interposed between contiguous neurons. However, as an outcome of recent research it is becoming evident that the

peculiar characteristics of reflex conduction upon which such stress has been laid in the past are manifestations of special modifying conditions of a non-essential nature at the reflex center and should not be taken to imply that the processes underlying the two types of conduction differ from one another in any fundamental way (see p. 821).

(1) *Summation*, temporal and spatial (See p. 811).

(2) *One-way conduction*—centripetal in the afferent and centrifugal in the efferent limb—as compared with two-way conduction in nerve fibers. The synapse may be compared to a valve or a gate which opens only one way. The irreversibility of conduction in the reflex arc was demonstrated in the early part of the 19th century by Bell and Magendie. The former (1811) showed that stimulation of the anterior roots cause muscular contraction, but no apparent effect followed stimulation of the posterior roots. Magendie (1822) found that stimulation of the posterior roots caused pain. These observations have been embodied in the so-called Bell-Magendie law which states that the anterior root fibers are purely efferent, those of the posterior roots purely afferent.

One-way conduction is not, however, an unalterable property of the synapse, for it is abolished by lowering the temperature of the spinal cord by a few degrees. It has been shown by Toennies, for example, that if the cord is cooled, stimulation of a dorsal root causes a discharge of impulses from the center which travel peripherally over a certain proportion of the fibers composing other dorsal roots, that is, antidromically (p. 235). Barron and Matthews have also found that cooling the cord causes muscular twitchings, and that each twitch is accompanied by a discharge of impulses along sensory root fibers.

(3) *Slower speed of conduction*, as measured by the latent period between the application of the stimulus to the afferent limb of the reflex arc and the response of the effector organ (e.g., contraction of a muscle). (p. 812)

(4) *Grading of the reflex response*. Variations in the strength of the stimulus cause corresponding gradations in the reflex response. When stimuli of gradually increasing intensity are applied in suc-

pression to a motor nerve the muscle shows step-like increases in response as a result of more and more nerve fibers being excited and of an increasing number of muscular units being brought into play, but after this an increase in the strength of the stimulus causes no greater effect ("all or none" principle, p. 785). In the case of the reflex response, increasing the strength of a single stimulus beyond that which brings all the afferent fibers into play may cause a further increase in the response of the muscle.

(5) As a result of a repetitive discharge from the center ("after discharge," p. 814) there is a lack of correspondence between (a) the moment of cessation of the stimulus and the termination of the response of the effector organ, and (b) the rhythm of the stimulus and that of the muscular response.

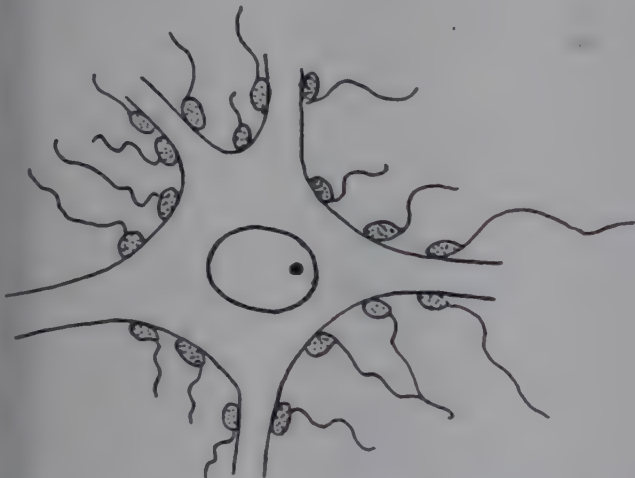


FIG. 333. Diagram showing "end feet" (*pieds terminaux*) making contact with the body of a nerve cell.

(6) *Greater variability in the threshold value* of the stimulus in the case of the reflex arc. The response to a given stimulus is influenced by conditions which do not come into play in the case of nerve fiber conduction, e.g., facilitation, recruitment, occlusion, etc. These will be considered later.

(7) *Susceptibility of reflex conduction to fatigue*, whereas nerve trunks are almost indefatigable.

(8) *Much susceptibility of reflex conduction to oxygen lack, anesthetics, shock, etc.* This is evidently due to the presence of the nerve cell in the conducting pathway. Nerve cells have a much higher metabolism than nerve fibers (p. 795) and reflex excitability is abolished if the centers are deprived of oxygen for a short period. The cells of the cerebral cortex are irreparably damaged if deprived of their blood supply for 5 minutes or so; in man deprivation of blood for even half a minute

may cause injury. The centers of the brain stem survive for a longer period—from 25 to 35 minutes, and the spinal centers for from 40 to 60 minutes. The autonomic centers are also relatively resistant to oxygen lack. According to Kabat, the resistance of the brain in very young animals (puppies up to 4 months of age) to circulatory arrest is much greater than is the adult brain. In deep *anesthesia* many reflexes are completely abolished, whereas nerve trunks remain excitable and may even respond to stimulation after an animal has been killed by an overdose of anesthetic. Ether vapor or other anesthetics applied *directly* to the nerve, however, quickly abolishes its excitability.

Some of the special features of reflex conduction mentioned above will be dealt with in more detail in the following pages. Certain other characteristic features of reflex action will also be considered.

Summation. The central excitatory state

Temporal summation. Though a single stimulus of a certain strength may, when applied to an afferent nerve or receptor organ, be unable to cause reflex contraction of a group of muscles, a response occurs if a series of such stimuli is applied to the nerve in rapid succession. This phenomenon is referred to as *temporal summation*. The shorter the intervals between the stimuli, which singly are inadequate, the greater is the reflex response; if separated by intervals greater than about 20 msec they are ineffectual. Such a result is best explained upon the assumption that each inadequate stimulus produces an excitatory state within the center; this state, though itself incapable of causing a discharge down the motor neuron (motoneuron), persists for an appreciable time and can sum with central excitatory states (C.E.S.) produced by the succeeding stimuli (see summation of inadequate stimuli, p. 781). Through such summation, the central excitatory state is raised to threshold value and a discharge occurs over the efferent neuron. A single impulse is rarely, if ever, able to give rise to a C.E.S. of threshold value. Temporal summation is well exemplified in the *scratch reflex* shown by the spinal dog (p. 829). This reflex, which consists of rhythmical scratching movements of the hind limb when the skin of the back is stimulated, cannot be elicited by the application of a single induction shock or even by two shocks unless they are very intense. The reflex is readily elicited by a series of rapidly repeated weak stimuli.

Sometimes the response does not occur until after the fortieth repetition (Sherrington). A single *mechanical* stimulus applied to the skin (e.g., plucking a hair, a pinch, etc.) may elicit the reflex, but under such circumstances it is probable that the receptor organ discharges a series of impulses (see p. 807).

In experiments involving direct stimulation of the oculomotor nucleus Lorente de N6 observed that increasing the interval between inadequate stimuli to more than from 0.1 to 0.2 msec. greatly reduced the summation value. The maximum summation effect was obtained when the stimuli were simultaneous. Since in these experiments the length of the interval at which any significant summation effect was observed is shorter than the relative refractory period of the afferent nerve fiber, considerable doubt has been raised as to the importance of temporal summation at any individual synapse. However, since the impulses in their course to the reflex center pass through internuncial neurons and are delayed in their passage through each synapse by from 0.5 to 2.0 msec., the anterior horn cell may be maintained in a state of subliminal excitation for a period up to 20 msec. A second inadequate stimulus applied to the afferent nerve during this time will raise the central excitatory state to threshold value.

Spatial summation. If two subthreshold stimuli are applied simultaneously, one to each of two afferent nerves, summation occurs and a response results. This type of summation, which is of essential importance in central excitation, is spoken of as *immediate spinal induction* or *spatial summation*. Allied reflexes mutually support or reinforce one another through such an effect. This therefore constitutes one type of *facilitation*. Immediate induction can also be readily demonstrated in the scratch reflex. When two subthreshold stimuli are applied within the receptive area of the reflex but about 10 cm. apart a response follows. Such a result, taken in conjunction with other observations which will be considered presently, indicate that the two afferent pathways converge upon and make connections with the same motoneurons.

Refractory periods

The nervous centers show an absolute and a relative refractory period, as well as a phase of supernormal excitability. The length of the absolute refractory period as observed by Eccles for the motoneurons of the flexion reflex is 2.5 msec. and from 10 to 15 msec. for the period of relative,

refractoriness. A lower value, namely 0.1 msec. was obtained by Lorente de N6 for the motoneurons of the more rapidly acting eye muscles. The refractory period is determined by applying strong stimulus to the undivided motor nerve of the reflex, and thus sending a volley of impulse backwards, that is, antidromically, into the spinal center. The antidromic volley causes discharge of the center just as though it had been stimulated through the afferent nerve. The succeeding interval during which the reflex cannot be elicited by stimulating the afferent nerve is the absolute refractory period. This is followed by a period of subnormal excitability—the relative refractory period.

Reflex conduction time

The time elapsing between the stimulation of the afferent nerve or receptor and the response of the effector organ is called the *total latent period* of the reflex. If from this be subtracted the time which the impulse would take in traveling over the afferent and efferent fibers (which conduct at rates from 80 to 100 meter per second) the time taken by the impulse to pass through the cord is obtained.¹ This is called the *central or reduced reflex time*. In the table given below the total latent period is 10.4 msec. and the total time of the peripheral pathways is 6.5 msec. leaving 3.9 msec. as the central reflex time. Since the length of the central pathway is only a small fraction of the length of the peripheral path while the central reflex time is nearly $\frac{1}{2}$ the total time, it is clear that the conduction rate through the center must be relatively very slow. The delay presumably occurs at the synapse and is attributed to the time required to build up the excitatory state to threshold value.

Total latent period.....	10.4 m. sec.
Time for passage of impulses in 13.8 cm. of afferent nerve at 31.6 meters per second...	4.4 m. sec.
Time for passage of impulses in 19.5 cm. of efferent nerve at 93 meters per second.....	2.1 m. sec.
Total time for peripheral path.	6.5 m. sec.
Therefore central reflex time (synaptic delay).....	3.9 m. sec.

—Modified from Creed, Brown,
Eccles, Liddell and Sherrington.

¹ If the time of arrival of the action current at the end of the efferent nerve is recorded the latency of the muscular response need not be considered.

When the interval between two stimuli applied to an afferent nerve is sufficiently brief the latent period of the response caused by the second stimulus is shorter than usual. The shorter latency cannot be attributed to a reduced conduction time in the peripheral nerve fibers; it must be central in origin, i.e., at the synapse. Now, the excitatory state rises to a maximum during a measurable time and declines again gradually. The reduced latency of the second volley of impulses is therefore attributed to their reaching the synapse before the effect of the first volley has disappeared; therefore a shorter time is necessary for building up the C.E.S. to threshold value. The synaptic delay under these circumstances may be reduced to 0.5 msec.

The delay is also greatly reduced by increasing the strength of the stimulus and may then be so slight that the conduction rate over the arc as a whole approaches that over nerve trunks.

Successive induction

This term is applied to the facilitation which one reflex exerts upon another immediately succeeding it. Successive induction may be *positive* or *negative*, that is, the second reflex reaction may be of the same sign as the first or of opposite sign. An example of positive successive induction is the augmentation of the scratch reflex which follows the successive stimulation of two separated points in the skin, as by rolling a spurred wheel over the surface. A parasite moving over the skin will exert a similar effect. Negative spinal induction is seen in rhythmical or alternating reflexes such as stepping, the shake reflex of the head or the biting reflex. For instance, the flexion reflex (contraction of flexors and relaxation of extensors of the limb) favors a succeeding extension reflex (contraction of extensors and relaxation of flexors) which in turn lowers the threshold for the next flexion reflex.

In the spinal animal (p. 828) spontaneous automatic stepping or scratching movements may occur which under favorable conditions persist for several minutes. Automatic stepping movements of the hind limb of the cat may persist even under deep anesthesia and after the opposite half of the cord of the segment supplying the limb has been destroyed. The reflex alternating movements are not abolished by deafferentation of the limb (section of posterior roots). The perpetuation of the rhythm is therefore not due to impulses arising in the contracting muscles; it is central (spinal) in origin.

Rebound

Allied to negative spinal induction is the phenomenon known as *rebound*. When, for instance, during the elicitation of a reflex, inhibition is induced by the stimulation of an afferent nerve, augmentation of the reflex occurs when the inhibitory stimulus is withdrawn (fig. 334). The rebound has a long latent period occurring about 0.2 second after the withdrawal of the inhibition. Sometimes the mere cessation of the stimulus which excited the reflex is sufficient, without inhibition, to cause rebound. It is most readily elicited in the crossed extension reflex of a decerebrate preparation. It is elicited with difficulty in the spinal animal. It is easily inhibited. It

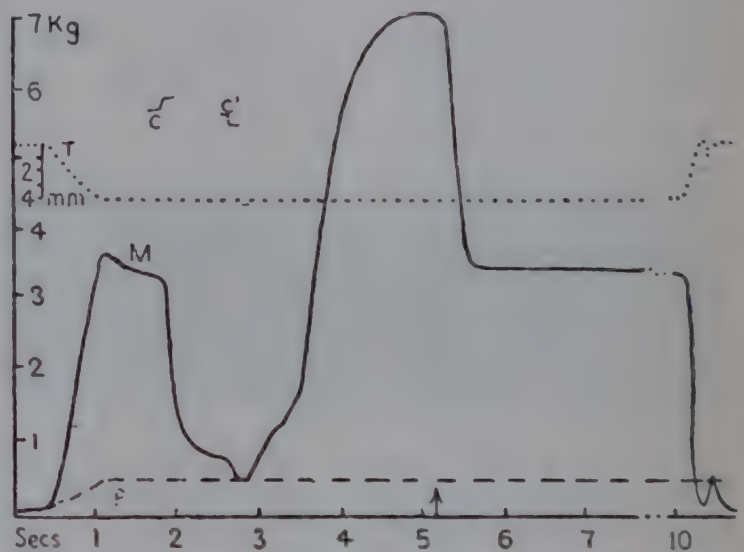


FIG. 334. Between *c* and *c'* the stretch-reflex of vastocrureus is inhibited by faradization of the peroneopliteal nerve of the same side. Note the inhibition and the further fall, "post-inhibitory notch" after *c'*. The post-inhibitory notch is followed by considerable rebound which in turn is inhibited at \uparrow by gentle traction on biceps femoris of the same side (from Creed, Denny-Brown, Eccles, Liddell and Sherrington, *Reflex Activity of the Spinal Cord*, The Clarendon Press).

appears after the silent period of a tendon jerk (p. 823) and, under certain favorable conditions, is followed in turn by inhibition and this again by rebound. Such a series of inhibitions and rebounds following the sudden stretching of a tendon and giving rise to automatic jerking movements is spoken of as *clonus*. The cause of rebound is not known with certainty. It is not due to proprioceptive impulses, since deafferentation of the muscle does not abolish it.

One explanation which has been offered is, that when the inhibitory stimulus is applied, excitatory afferent fibers as well are stimulated but their effects are masked by those of the inhibitory fibers. After withdrawal of the stimulus the persistence of the "after discharge"

of excitation beyond the inhibitory "after action" accounts for the augmented contraction. In certain rhythmical reflexes such as biting, rebound and negative successive induction apparently act together to increase the force of a contraction following a phase of inhibition. For example, electrical or mechanical stimulation of the gums or palate of a decerebrate preparation causes inhibition of the closers of the jaws (temporals and masseters), and contraction of the jaw-openers (digastrics). Immediately upon cessation of the stimulus, the jaw-closers contract powerfully. Thus, a rhythmic chewing reflex tends to keep itself going, so long as there is any material between the jaws upon which to bite (Sherrington).

After discharge

The discharge of impulses from the reflex center and the consequent prolongation of the reflex response after the stimulation of the afferent nerve or receptor has ceased is called *after discharge* (fig. 335). For example, the crossed exten-

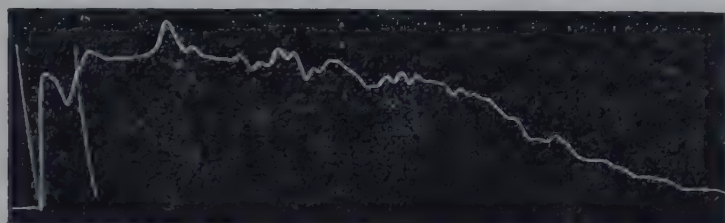


FIG. 335. Flexion reflex, showing *after discharge*. The duration of the stimulus is indicated by the pair of nearly vertical lines (after Sherrington).

sion reflex of the dog (extension of knee, ankle and hip following stimulation of the afferent nerve of the contralateral limb) may have, if the stimulus is very intense, an after discharge of a second or more. In other reflexes, e.g., the flexion and scratch reflexes, the after discharge is much shorter than this (60 to 70 msec.). After discharge is spoken of by Sherrington in a figurative sense as reflex "momentum." Increase in the strength or duration of the stimulus lengthens the after discharge. Increase in the intensity of the stimulus has a relatively greater effect upon the duration of after discharge than upon the amplitude of the contraction; after the latter has been increased to the maximum further strengthening of the stimulus lengthens the after discharge. After discharge is readily inhibited.

As a result of the after discharge from the spinal center a single stimulus applied to an afferent nerve is followed, not by a single twitch as when the motor nerve is stimulated, but by a series of twitches, an incomplete tetanus or even a complete tetanus. When a series of stimuli at a rate under

50 per second are sent into an afferent nerve the rhythm is just perceptible in the myogram whereas in the tetanus caused by direct stimulation of the motor nerve at the same rate the individual contractions are clearly visible. The smoothing out of reflex rhythm is due to the after discharge of impulses following each main volley, the tension of the muscle between the latter is thereby sustained.

After discharge is the result of the persistence and gradual subsidence of the excitatory state built up in the reflex center by the afferent nerve stimulation and the consequent repetitive discharge of impulses along the efferent fibers. The most probable explanation of the prolonged discharge is the one proposed by Forbes, namely that impulses are set up in certain long internuncial circuits and owing to the length of the course over which they must travel are delayed in their arrival at the motoneurons. It is unlikely that the asynchronous arrival of impulses at the center, due to different conduction rates of the fibers composing the afferent nerve or of variable delays at synaptic junctions, plays any important part; the after discharge is too long to be accounted for in these ways. The arrival at the center of impulses set up by the contracting muscle itself is of minor importance. If the afferent impulses from the muscle are blocked by sectioning the posterior roots (deafferentation) the after discharge is reduced though not abolished; it is therefore dependent, in part only, upon the re-excitation of the center by proprioceptive impulses.

Recruitment

Many reflexes gradually increase to a maximum when a stimulus of *unaltered* intensity is merely prolonged. This is due to the activation of a progressively greater number of motoneurons. The phenomenon is called *recruitment* and is figuratively spoken of as "*inertia*" by Sherrington. As already mentioned, "after discharge" is referred to as reflex "momentum." Both features neither of which is in evidence when the motor nerve is stimulated directly, obviously must give smoothness to reflex action. Recruitment is more easily demonstrated in decerebrate than in spinal preparations; it is well seen in the crossed extension reflex but not in the flexion reflex (p. 819). It is also seen in inhibitory reflexes, i.e., prolongation of inhibitory stimulus of constant strength causes the inactivation of an increasing number of motor neurons.

Irradiation

When the strength of a stimulus applied to a receptive area is gradually increased the central excitatory process spreads to a progressively greater number of motoneurons. As a consequence, additional muscle groups take part in the reflex response. The phenomenon is called *irradiation*. The impulses do not spread indiscriminately to all the motoneurons within a given radius of the point of entry of the afferent fibers; on the contrary, owing to the variability of the resistance at different synapses they are directed along selected paths. The synapses at the motoneurons in close proximity to the afferent terminals have the lowest threshold, but as the strength of stimulus is increased impulses spread farther afield and excite the neurons of adjacent and ultimately of more remote segments. For example, a weak stimulus applied to the sole of the hind paw of a decerebrate animal causes flexion of the ankle alone; upon gradually increasing the strength of the stimulus the knee flexes, then the hip (flexion reflex); later, extension of the crossed hind limb occurs (crossed extension reflex); extension of the ipsilateral forelimb follows and finally flexion of the contralateral forelimb. Besides the soles there are six other areas from which irradiation can be demonstrated very easily. These are the palms, the pinnae, the snout and the tail. The final attitude assumed when a stimulus of suitable strength is applied to the sole or to one of the other reflexigenous areas just mentioned is spoken of as a *reflex figure* (see fig. 336.) The spread of the irradiation (march of the reflex figure) in all cases follows a finite order. Upon stimulation of the pinna the order of spread is:—neck and ipsilateral forelimb, ipsilateral hind limb, contralateral hind limb, contralateral forelimb. The order upon stimulation of the hind limb (paw) is:—ipsilateral hind limb, contralateral forelimb, contralateral hind limb, ipsilateral forelimb.

It will be noted that only those muscles which contract synergically, that is, those which combine to effect a purposeful coördinated act, are activated. Muscles whose action is antagonistic to these are inhibited. The reaction which results corresponds to that which would occur from stimulation of the intact animal. Thus a painful stimulus of the hind paw causes withdrawal of the injured part, the other limbs reacting at the same time to support the body and move it from the stimulating agent. The reflex response is therefore quite

different from the response which would result from stimulation of an anterior nerve root—all muscles to which the fibers of the root were distributed would, of course, be activated.

Irradiation is reduced by spinal shock, anesthetics or diminished blood supply to the spinal centers. It is greatly increased by the action of such convulsant poisons as strychnine and tetanus toxin, which cause a general lowering of synaptic resistance; even a weak stimulus may then cause contraction of practically all the muscles of the body, antagonists as well as synergists.

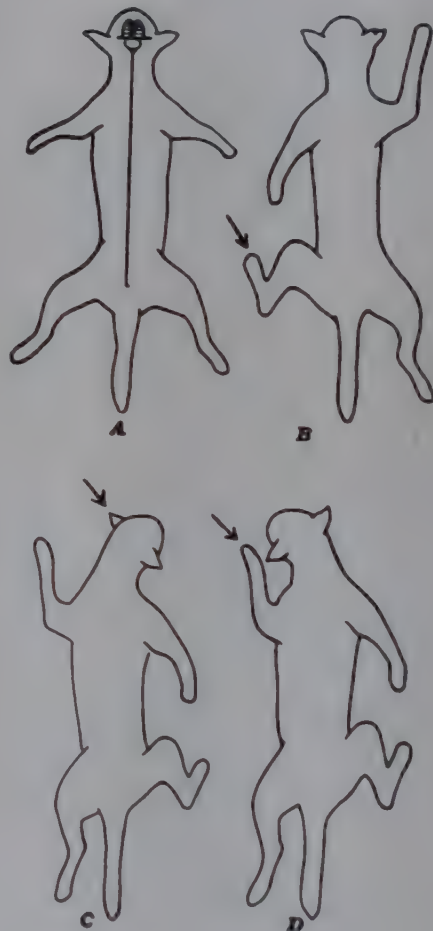


FIG. 336. Reflex figure. A, position of animal after decerebration; B, change in attitude from A caused by stimulation of left hind-foot; C, change in attitude caused by stimulation of left pinna; D, attitude resulting from stimulation of left fore-foot (after Sherrington).

Fractionation of the reflex center

When an afferent nerve is stimulated by a faradic current of *gradually increasing* intensity the tension developed by the reflex contraction increases to a point after which increase in the strength of the stimulus fails to augment the reflex tension. The limitation is not simply due to all the motoneurons of the reflex having been excited, for direct stimulation of the motor nerve causes a development of tension greatly in excess of that resulting from the stimulation of the single

afferent nerve. It is concluded that under the ordinary conditions attending reflex action, a single afferent nerve when stimulated activates only a fraction of the motoneurons supplying a given muscle. The size of the fraction of the motoneurons governed by the afferent nerve varies under different conditions; it is reduced by fatigue, oxygen lack, anesthesia, etc., and increased by the administration of a small dose of strychnine. Even under the most favorable conditions, however, the number of motoneurons excited through a single afferent nerve is not more than a fraction of those which can be excited by stimulating the motor nerve.

TABLE 76

MUSCLE	AFFERENT NERVE STIMULATED	MAXIMUM REFLEX TENSION	MAXIMUM REFLEX TENSION IN PER CENT OF MAXIMUM MOTOR TENSION
		grams	
Tibialis anticus	Internal Saphenous	800	32
	Ext. Cut. of groin	1,060	37
	Superf. obturator	165	6.7
	Deep obturator	400	16
	N. to quadriceps and Sartorius	1,190	44
	Small sciatic	1,320	45
	Popliteal	1,820	78
Semitendinosus	Internal Saphenous	1,900	63
	Ext. Cut. of groin	830	28
	Superf. obturator	1,270	42
	N. to quadriceps and Sartorius	2,740	91
	Small sciatic	?	62

Furthermore, the motor units² excited through one afferent nerve do not lie in a single muscle, but are distributed throughout many different and often widely separated muscles. In table

² By a "motor unit" is meant a single motor neuron and the bunch or "squad" of about 100 muscle fibers which it supplies. Close to the muscle and within it, each nerve fiber divides dichotomously into several daughter fibers, each of which ends in one of the 100 or so muscle cells. The semitendinosus muscle of the cat has some 630 such motor units, the gastrocnemius medius 430, the extensor longus digit 330 and the soleus 250. By dividing the total tension developed in a muscle during maximal stimulation of its motor nerve by the number of motor units, the average contraction tension of a single motor unit, is obtained. The values found by Eccles and Sherrington were 5.5, 30.1, 9.9, 8.6 grams respectively for the semitendinosus, gastrocnemius medius, soleus and extensor longus digit.

76 are shown the reflex tensions developed respectively in the tibialis anticus and semimembranosus as a result of stimulation of various afferent nerves. In the last column these tensions are given as percentages of those developed by direct stimulation of the motor nerves (motor tension). It will be noted that the fraction of the motor unit activated by the different afferent nerves varies widely, those nerves more closely allied segmentally to the motor innervation involving a larger proportion of the units of the muscle than those more remote.

The principle of convergence; occlusion

Evidence that a given group of anterior horn cells is in communication with the central terminals of more than one afferent nerve has already been cited in the paragraphs dealing with spinal induction. This principle of convergence of afferent pathways is shown in other ways. For example if a muscle be strongly excited by the successive stimulation of two afferent nerves it is found that the sum of the reflex tensions developed in the two responses is much greater than the maximum tension developed after a single stimulation of the motor nerve. Obviously there must be a central overlap of the two afferent pathways—a proportion of the motoneurons supplying the muscle must be connected with both.

Also, the sum of the reflex tensions developed when strong stimuli are applied to two afferent nerves successively is often found to be considerably greater than the tension resulting from stimulation of the two nerves simultaneously. The difference in the tension values is called occlusion. For instance, the sum of the tensions developed in the tibialis anticus when the two plantar nerves (afferent) are stimulated consecutively is 3.15 kgm. (1.57 + 1.58 kgm.) whereas the tension following simultaneous stimulation of the same nerves is only 1.81 kgm. (no more than 15 per cent greater than that resulting from the stimulation of one nerve). The occlusion therefore amounts to (3.15 - 1.81) = 1.34 kgm. This result is not due to interference of one afferent pathway with the other, or to inhibition. It is simply due to the fact that a certain proportion of the motoneurons of the reflex is common to the two afferent nerves; the motoneurons common to the two afferents are excited maximally by either nerve alone, so no greater effect upon the muscle can be produced by exciting them through both afferents simultaneously. Occlusion is there-

fore a measure of central overlap, i.e., of convergence of afferent paths (fig. 337A).

Not only in reflexes set up through afferent nerves of similar function and distribution does occlusion occur; it is also evident between reflexes resulting from stimulation of such dissimilar nerves as the internal saphenous and the nerve to the sartorius. The smoothness of reflex action, the interlocking of allied reflexes, the gradual, even passage from one reflex to another and the general coördination of muscular function are the natural consequences of, (1) the fractional control by any one afferent of the centers governing the muscles of a given reflex, and (2) the overlap of the motoneuron fields of afferents governing different reflexes.

"SUBLIMINAL FRINGE." Increasing the strength of the stimulus increases the extent of the central overlap and so of the occlusion. When, on the other hand, the stimulation is weak, occlusion may be absent and the sum of the tensions resulting from the concurrent stimulation of the two afferents will then be greater than the tension developed when they are stimulated successively, i.e., instead of there being a deficit of contraction there is actually augmentation (facilitation). The reason for this will be made clear by reference to figure 337. Strong stimuli set up effective excitatory states in the motoneurons connected with each afferent path; these excitatory fields overlap and concurrent stimulation of the two afferents results in occlusion as just described. Fringing the effective excitatory field (*liminal field*) is a zone in which the excitatory state is beneath the threshold for the discharge of impulses down the motoneurons. This is called the *subliminal fringe* (it is not shown in fig. 337 A). When the stimuli are weak the liminal fields are less extensive and so do not overlap (fig. 337 B). Overlapping of the *subliminal fringes* of the two afferents, however, causes through summation the excitatory state of the overlapped neurons to be raised to the threshold level. Thus motoneurons which are unexcited by either stimulus alone, are excited when both are applied together. The response which results when subthreshold stimuli are applied simultaneously to two afferent nerves (immediate spinal induction) may also be explained by the overlap of subliminal fields.

That subliminal fringes surround excitatory states produced by *maximal* as well as those produced by weak stimulation is shown by the following experiment. Strong faradization of the central end of the internal saphenous nerve causes tetanic contraction of the tensor fasciae femoris. A single break shock applied to the

musculo-cutaneous nerve induces a reflex contraction which lasts for $\frac{1}{2}$ second. Stimulation of the musculo-cutaneous *during* the tetanic contraction induced by the stimulation of the internal saphenous causes an aug-

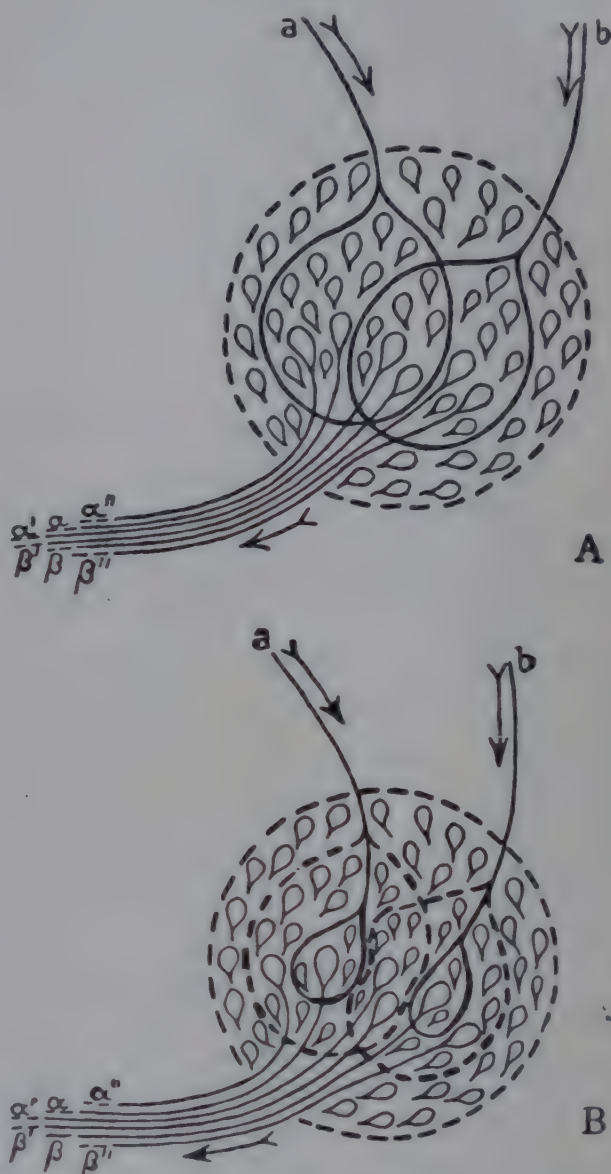


FIG. 337. A, illustrating occlusion. *a* and *b* are two afferent fibers; *a* when stimulated alone excites the motoneurons within the outlined area; only four motor fibers (α'' , α , α' and β') are represented. *b* when stimulated alone activates the motoneurons in the corresponding area, of which four axons (β' , β , β'' and α') are shown. Thus when the two afferents are stimulated consecutively the motoneurons α' and β' are activated each time, making a total of eight. When stimulated concurrently the total number of activated motoneurons is six, i.e., there is a deficit of contraction due to occlusion. B, weaker stimulation of the afferents *a* and *b*, restricts the respective fields of threshold excitation as shown by the continuous line limit. *a* by itself activates one motoneuron α ; *b* activates β . Concurrently they activate four units (α' , α , β' and β) owing to the summation of the subliminal effect in the overlap of the subliminal fields outlined by the broken lines (from Creed, Denny-Brown, Eccles, Liddell and Sherrington, *Reflex Activity of the Spinal Cord*).

mentation of the contraction which persists for $\frac{1}{2}$ second. The facilitation is attributed to the subliminal fringe caused by stimulation of the musculo-cutaneous being overlapped, and so raised to threshold value, by the

subliminal fringe caused by stimulation of the internal saphenous.

The subliminal fringe provides a mechanism for the linking together of allied reflexes having origins close together or widely separated. It provides a background or, as Sherrington expresses it, a "catch on" for labyrinthine and other types of reinforcement. Stimulation of certain areas of the cerebellum, for instance, produces no effect itself upon limb movements, yet can modify reflex movements already in progress. Again, afferent stimuli too weak to elicit a limb reflex become effective when neck and labyrinthine proprioceptors are stimulated by turning the head, though this movement itself causes no apparent effect. The facilitation of one phase of an alternating reflex by the other (p. 813) is also attributed to the overlap of subliminal fringes persisting for a short period after each phase.

The principle of the final common path

Each fiber composing an afferent nerve is a pathway for impulses arising in a limited number of receptor organs (p. 797). The afferent nerves are private paths through which the receptors communicate with the spinal centers. The motoneurons of a given reflex, on the other hand, are as public roads which must accommodate traffic from a large number of differently located points; upon them impulses from many and various receptive areas of the body converge. This final link in the reflex arc, the motoneuron, is therefore called the *final common path*. Each final common path (F.C.P.) is as the stem of a funnel of which the numerous afferent paths represent the expanded portion (see fig. 326, p. 798 and fig. 338). Conversely, each afferent nerve can communicate with a great many F.C.P.'s. Potentially, every afferent fiber is in communication with all F.C.P.'s. After strychninization, for instance, or the injection of tetanus toxin, a stimulus applied to practically any region of the body induces wide-spread muscular contractions (convulsions). Since all reflex action of muscle is brought about through impulses traversing the final common path, this must subserve a variety of reflex responses. At the entrance to the final path, i.e., at the convergence point of the afferent pathways, excitatory and inhibitory states are set up. It is upon the nature and extent of these that the type and intensity of the resulting reflex depends.

Allied reflexes, i.e., those conjoining to effect

a common purpose, use the path concurrently to reinforce one another. Such reflexes may originate in widely separated regions and from diverse receptors (receptors of skin, eyes, organs of smell, muscle and labyrinthine proprioceptors, etc.). For example, stimulation of the outer digit of the hind foot causes reflex flexion of the same limb. If other digits are stimulated concurrently, the flexion reflex occurs more readily (facilitation, p. 812). Additional stimulation of the contralateral fore foot or pinna or of the tail further reinforces the flexion response.

Antagonistic reflexes, on the contrary, cannot occupy the final path simultaneously; the most important of two such reflexes must give way. For example, during the scratch reflex a strong stimulus is applied to an afferent nerve of the limb

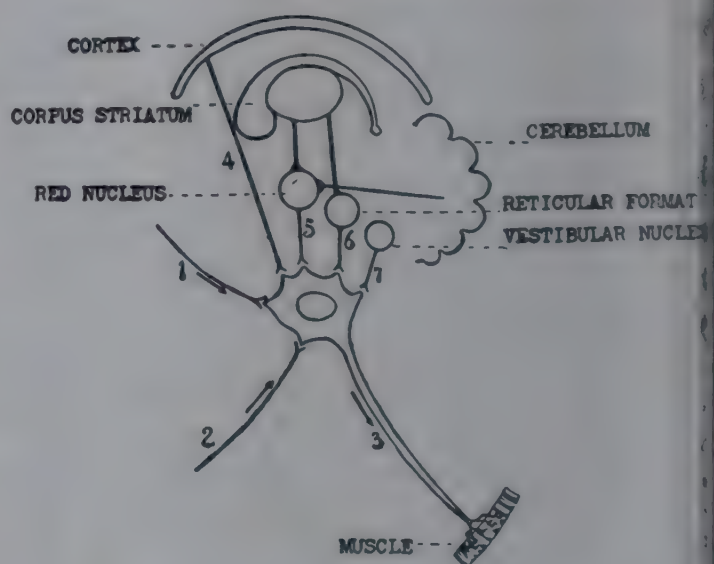


FIG. 338. Diagram showing the convergence of various paths upon the anterior horn cell. 1 and 2, afferent fibers from periphery; 3, motoneuron (final common path); 4, corticospinal fiber; 5, rubrospinal fiber; 6, reticulospinal fiber; 7, vestibulospinal fiber. Part from Lennox and Cobb, redrawn and modified.

engaged in the scratching movements, the limb becomes strongly flexed, i.e., the scratch reflex gives place to the flexion reflex. Protective reflexes, e.g., those set up by injurious agents are accompanied by pain in the conscious animal and are prepotent, displacing less urgent responses from the final common path. The flexion reflex (see below) which withdraws the foot from a noxious influence is a reflex of this nature.

Reciprocal innervation

Voluntary or reflex contraction of a muscle, e.g., the biceps, is accompanied by the simultaneous relaxation of its antagonist—the triceps. Reciprocal innervation of antagonistic muscles is illustrated by the following experiment. When

the paw of a spinal or decerebrate animal (p. 825) is pinched, pricked, burned or stimulated by a strong electric shock, or the central end of the peroneal nerve excited, there results in the same limb a strong contraction of the flexor muscles of the ankle, knee and hip, together with inhibition of the extensors. This is the *flexion* or *withdrawal* reflex. In the contralateral limb the picture is reversed. There occurs contraction of the extensors together with inhibition of the flexors—the *crossed extension reflex* (fig. 339 and

the extensors, and the limb, if it be in such a position that it can be acted upon by gravity flexes at the knee. (Reciprocal innervation of the eye muscles is described on page 1017).

The inhibitory effect upon the skeletal muscles is not brought about through specific inhibitory nerves as in the case of cardiac inhibition (vagus) or of the inhibition of the intestine (sympathetic). Direct stimulation of a muscular nerve results only in excitation. The inhibitory process is therefore central in origin. The reciprocal inhibition of



FIG. 339. Reciprocal action of antagonistic muscles. Record from leg of a decerebrate cat; F, flexor; E, extensor. The myograph writer for the extensor muscle is set a little to the right of that for the flexor muscle in order that the two may clear each other. The ascent of F and the descent of E are actually synchronous (from Sherrington).

340). The purpose in these reflex reactions is obvious; when an animal's paw is painfully stimulated the flexor muscles contract to withdraw the limb while contraction of the extensors of the opposite limb stiffen it for the support of the body.

The reciprocal inhibition of the knee extensors in the flexion reflex may be demonstrated more clearly after abolishing the action of the flexor muscles by sectioning their tendons; stimulation of the afferent nerve is followed by relaxation of

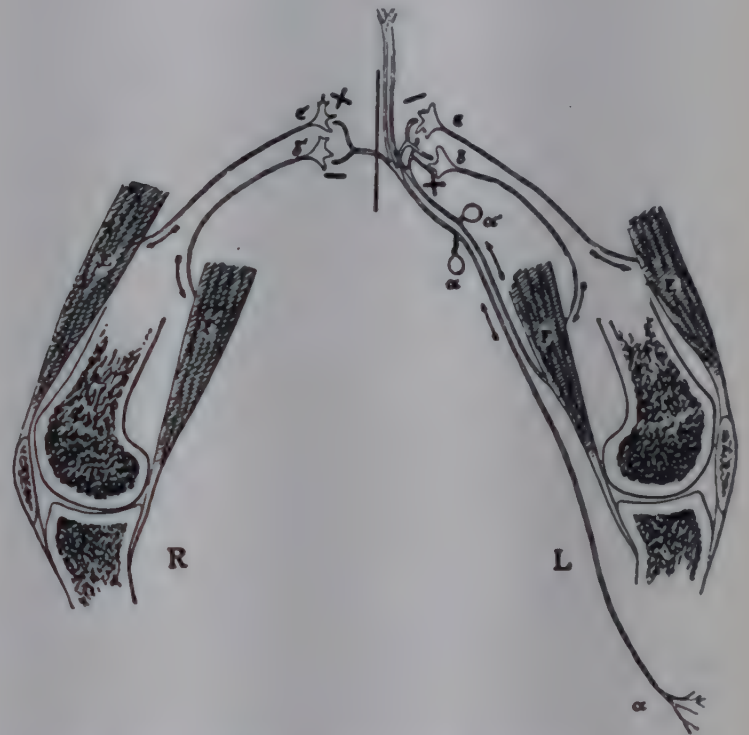


FIG. 340. Diagram illustrating reciprocal innervation. The afferent fibers (α) from skin of leg and (α') from the flexor muscles of the knee (in hamstring nerve) pass to the spinal cord, where each divides into two. One division goes to a motoneuron (ϵ) of the extensor muscles (E) and the other to a motoneuron (δ) of the flexor muscles (F). A branch of each afferent also crosses the mid-line to similar motoneurons (ϵ' and δ') on the opposite side of the cord. The afferent impulses, as indicated by the plus and minus signs either excite or inhibit the motoneurons, the respective effect being a function of the synapse. For the sake of simplicity internuncial neurons between the afferent and efferent neurons have been omitted (after Sherrington).

muscles which results from the stimulation of an afferent nerve is due simply to the cessation of excitatory impulses along the motoneuron, which may result, as suggested by Gasser, from certain connecting (internuncial) neurons having entered the phase of subnormal excitability. This phase corresponds to the positive after potential as recorded from the cord (p. 789).

Central inhibition

Examples other than the one mentioned in the last section may be cited and will serve to illustrate

certain features of the central inhibitory process. If during the progress of a flexion reflex a contralateral nerve is strongly stimulated the reflex is inhibited. Or, if the contralateral nerve is stimulated by a single break shock a short time *before* a similar shock is applied to the ipsilateral nerve, the after-coming flexor response is reduced. The degree of inhibition brought about depends not only upon the strength of the inhibitory (contralateral) stimulus itself but is related inversely to the strength of the excitatory (ipsilateral) stimulus. In other words, one effect is pitted against the other and the algebraic sum of the two opposed effects determines the intensity of the flexor response. The extent of the inhibitory effect caused by the contralateral stimulation is related to the length of the interval by which it precedes the ipsilateral stimulation. The maximal inhibitory effect is obtained when the interval is about 50 msec. (30 to 80 msec.). Shortening or lengthening the interval reduces the inhibition so that it is absent if the interval is less than about 6 msec or greater than 200 msec or so. The absence of the inhibitory effect when the interval is short, is ascribed to the slow development of the inhibitory as compared with the excitatory state. The diminution in the effect as the interval is lengthened is attributed to the subsidence of the inhibitory state before the excitatory state has been developed.

Several other examples of central inhibition have been demonstrated recently. Thus, the discharge of impulses set up in the motoneurons to the vastus internus muscle by stimulation of the 6th L. posterior spinal nerve root, is inhibited by concurrent stimulation of the 7th L. posterior root (Renshaw).

Inhibitory, like excitatory effects, undergo summation; varying degrees of inhibition are therefore possible. For example, two inhibitory stimuli, applied a short interval apart (less than 60 msec.) to an afferent nerve cause a greater effect than does one alone, and a series of inhibitory volleys causes a gradually increasing inhibition. Summation of inhibition also results when the two contralateral nerves are stimulated simultaneously or at a short interval apart. The principles of convergence and overlap of liminal and subliminal fields (p. 817) apply, apparently, to inhibitory as well as to excitatory states. Fractionation of the reflex center in regard to inhibition analogous to that described for excitation (p. 815) also apparently exists. Inhibition shows recruitment (p. 814) and an after action

analogous to the after discharge of excitatory states (p. 814).

No satisfactory theory has yet been formulated to explain central inhibition. The relatively prolonged nature of the inhibitory process suggested that a chemical mediator of some kind is responsible, but there is no evidence to support such an idea. The theory of Wedensky has been called upon to account for central inhibition but its inadequacy is generally accepted. Certain types of central inhibition, for instance that of the flexion reflex, appear to be due to impulses falling in the subnormal phase which are too weak themselves to cause a response yet to block excitatory impulses.

The nature of central excitatory (C. E. S.) and central inhibitory (C.I.S.) states

Sherrington and his associates have given a new conception of central nervous activity. According to this school, the reflex centers should no longer be looked upon as exchanges where impulses arriving at the afferent terminals are merely "switched" to the appropriate efferent paths. Afferent impulses upon their arrival at the motor neurons (i.e., at the synapses) create central excitatory states (C.E.S.) of longer duration than the impulses themselves and are capable of summation; or central inhibitory states (C.I.S.) are produced which can sum likewise. As a result, the reflex center is capable of discharging at its own rhythm and of grading its response though the impulses which it receives are "all or none" in character. The sign and intensity of the resulting reflex action is dependent upon the relative values of these states developed at the motoneurons of the final common path. If the C.E.S. is of subthreshold value a discharge of impulses does not result. As soon as it rises above the threshold value a discharge of impulses occurs; for this reason it is not possible to build the C.E.S. above threshold value. The frequency of the impulses and so the magnitude of the reflex response is dependent upon the rate at which the C.E.S. is built up. It has already been mentioned that a single impulse is rarely, if ever, capable of raising the C.E.S. to threshold value, the summation of the effect of two or more impulses being necessary. If the C.E.S. is antagonized by the C.I.S. the central excitatory state is reduced or completely abolished. The C.E.S. takes a certain length of time to develop to threshold value, the inhibitory state a longer time. Each persists for an appreciable period during which its intensity

gradually diminishes; the C.I.S. lasts for a longer time than does the C.E.S.

The C.E.S. accumulated as a result of afferent impulses is dissipated by an antidromic volley; this is shown by the following experiment. When two single shocks of equal intensity and separated by a short interval are applied to an afferent nerve, the second response is greater than it would have been had it not been preceded by the first (facilitation). If between two stimuli (and about 18 σ after the first) the motor nerve³ of the muscle be stimulated so as to "back" a volley of impulses into the reflex center, i.e., antidromically, the second response shows little or no facilitation. The annulment of the facilitation is ascribed to the inactivation of the C.E.S. formed by the afferent volley in the subliminal fringe of the motor neurons (p. 817). Also an antidromic volley set up during the after discharge of the flexor reflex is followed by a period of quiescence lasting for 20 msec to 50 msec,⁴ that is, the after discharge is cut short, due to inactivation of C.E.S.

Whereas C.E.S. induces a discharge of impulses down a motoneuron, the development of C.I.S. results in a cessation of impulse discharge. An antidromic volley has no effect upon C.I.S. The central inhibitory state is therefore looked upon simply as the inactivation of the central excitatory state, having no direct effect upon the motoneurons. In other words, if central inhibition exists, the antidromic volley finds C.E.S. already inactivated and so can produce no other effect.

The overlap of excitatory fields has been considered (p. 316). Overlap of an excitatory field by an inhibitory field is indicated by the following observation. A weak inhibitory stimulus pitted against a weak excita-

The posterior spinal roots of the nerve are sectioned in order to block any afferent impulses.

The antidromic volley, it is believed, does not pass beyond the surface film interposed between the motoneuron and the afferent terminals, i.e., the synapse. The latter is therefore considered to be the site where accumulation of C.E.S. occurs.

tory stimulus frequently fails to reduce the latter's effect. If, however, the *excitatory* stimulus is increased, then the weak inhibitory one is definitely effective. This result is best explained by the conception that the excitatory field has been enlarged by the stronger stimulus and so has been overlapped by the inhibitory field.

The nature of the fundamental process underlying the central excitatory state and transmission across the synapse has been a subject of speculation and controversy for a number of years. The question has not received a final answer but recent research has contributed several important facts leading to considerable clarification. It has been taught for many years that certain phenomena, e.g., one way conduction, temporal summation, latency and the transmission of impulses across a non-conducting gap (the synapse) were peculiar to reflex action and dependent upon the specific properties of the synapse. However, all of these phenomena can be demonstrated in the nerve fiber and it is becoming more and more evident that synaptic transmission and nerve fiber conduction are basically similar, the differences are of a minor character and can be explained largely by differences in organization and time relationships. Keith Lucas' conception of the synapse as a region of decrement probably comes nearer to the truth than any other. The role played by acetylcholine in central excitation is also now thought to be essentially the same as that which it plays in excitation of the nerve fiber. This subject will be dealt with in Chapter LXXIII. We shall see there that the electrical and chemical theories of synaptic (and neuromuscular transmission) can be reconciled, for the action potential and the production of acetylcholine appear to be closely related phenomena, indeed, interdependent parts of the same basic process.

CHAPTER LXVI

THE PHYSIOLOGICAL MECHANISMS GOVERNING POSTURE AND EQUILIBRIUM

STRETCH OR MYOTATIC REFLEXES

The reflex contraction of a healthy muscle which results from a pull upon its tendon is called the stretch or myotatic reflex. Any attempt to flex the limb of a decerebrate preparation, for example, meets with considerable resistance. This is due to the reflex contraction of the extensor muscles whose receptors (muscle spindles) are sensitive to a stretch stimulus (p. 805). After the section of either its motor or afferent nerve the response is very greatly reduced, the muscle then offering little resistance to passive flexion. In figure 341 are shown records of the reflex response to stretching the knee extensor (quadriceps) before and after section of its motor nerve. Liddell and Sherrington found that stretching the muscle by as little as 0.8 per cent of its original length was sufficient to evoke a reflex response. The tension developed may amount to as much as 2,000 grams. Slow as well as rapid stretching of the muscle elicits the reflex. The strength of the contraction continues to increase within limits so long as the stretching force increases; this fact, in view of the results of Adrian and of Matthews (p. 806), is probably due to a rise in frequency of the discharge from individual muscle receptors (muscle spindles) as well as to more of these being stimulated—*peripheral recruitment*—the force of the muscular contraction is thus automatically adjusted to the degree of stretching force applied.

A stretch of constant degree causes a maintained steady contraction, the muscle spindles and the stretch receptors in tendons showing very slow adaptation (p. 807). The reflex ceases immediately upon withdrawal of the stretching force, i.e., it shows little or no after discharge (p. 814). Its latent period is short, less than 20 m. sec. It is readily inhibited by stimulation of an ipsilateral or contralateral afferent nerve or by stretching the antagonistic flexor muscle; overextension in the intact animal is thus automatically prevented. The stretch reflex is obtained predominantly from those muscles which maintain the body's posture, e.g., quadriceps, soleus, gastrocnemius and other extensors. In the decerebrate animal flexors show little or no response to steady stretch, but in the intact or thalamic animal the flexors also exhibit

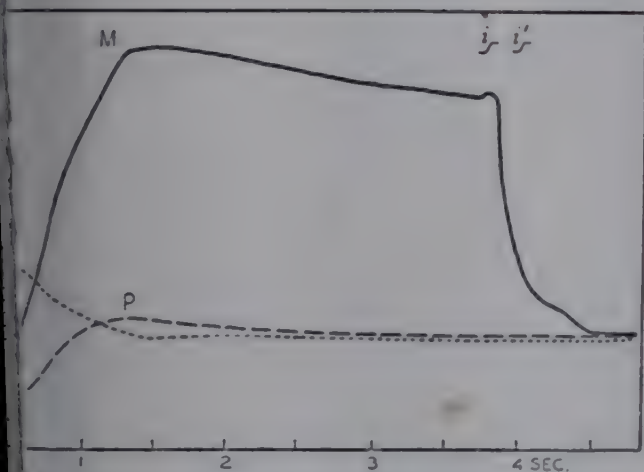
these reflexes (see supporting reactions). labyrinthine and neck reflexes exert their effect upon the limb muscles, chiefly, through the forcement of myotatic reflexes.

The knee and ankle jerks

A sharp tap upon the patellar tendon, when the knee joint is semi-flexed and the leg dependent causes a short twitch of the knee extensor. A blow upon the tendo Achillis causes a contraction of the calf muscles. These contractions or jerks, as well as those described below for the upper limb, are "fractional examples of the stretch reflex" and are not due to stimulation of the tendon or to direct stimulation of the muscle. The tap causes a sudden momentary stretch of the muscle (a stretch of 0.05 mm less in $\frac{1}{20}$ second being sufficient to elicit the response). Rendering the tendon itself insensible by means of cocaine does not prevent the response. A voluntary action, such as clasping the hands together, reinforces the reflex and increases the force of the jerk. *Patellar or ankle clonus* consists of a rapid rhythmical series of twitches of quadriceps or calf muscles, respectively, which results from the application of a sudden stretch stimulus when, as in a lesion of the pyramidal tract, the reflex arc concerned is abnormally excitable. A sharp depression of the patella by the examiner or a sharp dorsi-flexion of the ankle elicits the respective clonic response. The center for the knee jerk in the human subject lies in the 2nd, 3rd and 4th lumbar segments of the cord; it is innervated through the anterior crural nerve. The center for the ankle jerk is situated in the 1st and 2nd sacral segments; the peripheral nerve is the sciatic.

For a long time the knee jerk was thought to be a direct response of the muscle and not a reflex since its latent period was only some 6 to 12 m. sec. The revised estimates of the speed of conduction in peripheral nerve (up to 100 meters per second) show that this time is not too short for the occurrence of a purely spinal reflex, which the knee jerk is now generally accepted to be. Johnstone found the reduced reflex time (p. 812) to be only 2 m. sec. Any condition, such as decerebration

to the pyramidal tracts (p. 863), which increases the stretch reflexes increases the tendon jerks. They are abolished by an injury or disease involving the efferent or afferent limb of the reflex or the center itself (anterior horn cells). On account of its brief twitch-like character the knee jerk is sometimes spoken of as the "phasic reaction" of the stretch reflex, whereas the sustained contraction resulting from a continuous pull upon the tendon, and which is concerned in the maintenance of posture, is referred to as the "static postural reaction" of the stretch reflex. The jerk is less subject to abnormal states, e.g., spinal transection, anesthetics, circulatory failures, than are the postural reactions. In an animal such as the dog or rabbit, the knee jerk is absent in a few minutes after spinal transection,



341. The stretch reflex of the quadriceps (cat). M is the response (M) before and (P) after cutting the muscle. T is a record of the table-fall stretches the muscle. At the right is shown the reflex inhibition, evoked between i and i' by stimulation of afferent fibers in the ipsilateral peroneo-nerve (from Liddell and Sherrington).

monkey after some days. In man, though reflex activity is entirely lost, the muscles are quite flaccid, the knee jerk is elicitable in man free in from 3 to 7 weeks after a complete lesion of the cord (see p. 870).

Tendon reflexes of the upper limb

are the biceps, triceps and supinator jerks. The *biceps jerk* is elicited by a sharp tap upon the tendon; the response consists of a quick contraction of the biceps with flexion of the elbow. The center for the reflex is situated in the 5th

and the electrical responses are recorded from the animal during the elicitation of a tendon jerk. The contraction of action currents is found to occur at the actual contraction of the muscle. This, the "silent period" is probably due to the muscle spindles being relieved of stretch as the muscle contracts (see p. 805).

and 6th cervical segments of the cord; it is innervated through the musculocutaneous nerve.

The *triceps jerk* is evoked by a blow upon the triceps tendon just above the olecranon process of the ulna; contraction of the muscle and extension of the elbow result. The center for the response lies in the 6th and 7th cervical segments; the peripheral nerve is the musculospiral (radial).

The *supinator jerk* consists of contraction of the supinator muscle and flexion of the elbow; it follows a blow upon the styloid process of the radius. The center lies in the 5th and 6th cervical segments of the cord; the peripheral nerve is the musculospiral.

THE TONE OF SKELETAL MUSCLE

As a result chiefly of the work of the Sherrington school the word "tone" or "tonus" as applied to skeletal muscle has acquired a clearly defined meaning which previously it had lacked. Muscle tone is the steady reflex contraction which resides in the muscles concerned in maintaining the posture characteristic of a given animal species. To use Sherrington's words "reflex tonus is postural contraction." Tonus has its basis in the "static reactions" of the stretch reflexes, and its seat is therefore mainly in the *antigravity muscles*. In most mammals these are extensor muscles and we shall see that in decerebrate rigidity the animal exhibits an attitude which is a caricature of standing, due to an exaggeration of the tone of the extensors.

In man the antigravity muscles and consequently those which exhibit the greatest degree of tone are the retractors of the neck, the elevators of the jaw (masseters), the supraspinatus, the extensors of the back, the ventral muscles of the abdominal wall (probably), and the extensors of the knee and ankle (vastocruureus, gastrocnemius and soleus). When these muscles are completely relaxed, as in an unconscious person, the body collapses. In the healthy conscious person, stretch reflexes are largely instrumental in preventing this occurrence for, as we have seen, the elongation of an antigravity muscle by less than 1 per cent of its length stimulates the muscle spindles and a sustained reflex contraction results (see also supporting reactions, p. 833).

Though the fundamental basis of tonus in voluntary muscle is the myotatic reflex centered in the cord, the tonus state is influenced profoundly by higher centers. Impulses from labyrinthine and neck muscle receptors (p. 830) exert their influ-

ence upon this background of tonus established through lower spinal centers. Similarly, pathways from cerebellar, midbrain and cerebral centers convey impulses which, impinging upon the final common path, are capable of altering the degree of tonus, of effecting finer adjustments in the tonus state and of maintaining a normal distribution of tonus between groups of muscles (fig. 338, p. 818). The tone of a given group of muscles may also be influenced through the spinal centers by impulses arising in other muscle groups (e.g., neck muscles and the muscles of the digits, ankle and wrist, as in the positive supporting reaction) and in skin receptors.

When the spinal centers are separated from higher centers, extensor tone is abolished (see spinal shock, p. 828). Also, since it is dependent upon stretch reflexes, muscular tone is lost after injury to the afferent or efferent nerves, or to the center itself.

A feature of tonic contraction is its economy in the expenditure of energy. Posture is maintained for long periods with little or no evidence of fatigue, e.g., in decerebrate rigidity; in the maintained closure of the jaws, standing or sitting in the normal person; and in the clasping reflex of the frog. The increase in metabolism is less than in the case of those ordinary contractions which result in movement, though the difference is not as great as was once supposed.² It had also been thought that tonic contractions were unaccompanied by action currents. This, however, has been shown to be an error. The work of Forbes and of Adrian and their associates indicates that the economy of energy is effected through different groups of muscle fibers contracting in relays, only a proportion of the total number of fiber groups of the muscle being active at any moment. Thus, active groups mingled with inactive groups are scattered throughout the muscle. The alternating periods of rest and activity of the muscle groups explains the ability of the tonic contraction to be maintained for so long without showing fatigue.

Red and white muscle

The skeletal muscles of many animals, e.g., birds, rabbit, cat, etc., can be clearly divided into two types,

² In the normal human subject postural contractions cause a rise of from 50 to 70 per cent in the basal metabolism. In certain nervous states, in which the body is maintained in fixed attitudes for long periods (catatonial), the increase in metabolism resulting from the tonic contraction of the muscles is less (20 per cent) than in the case of the normal subject. The circulatory effects of sustained posture are also less pronounced in the pathological cases (Gayler and Wishart, *Brain*, 1933, 56, 282).

(a) *red or dark*, and (b) *white or pale*. The former, compared with the latter, are composed of fibers having a granular and more opaque appearance, possessing more distinct longitudinal striations but less pronounced cross striations, and containing a larger proportion of sarcoplasm.³ The *red* fibers contract more slowly, fatigue less readily, and are tetanized at a slower rate of stimulation than are the *pale* fibers. The *pale* fibers are translucent, show prominent cross striations and a small quantity of sarcoplasm. Muscles which execute rapid movements are usually composed of the pale variety, whereas muscles which execute slower movements are carried out chiefly by the red fibers. It is probable that all muscles are a mixture of the two types of fiber, but that in some the red type predominates, and in others the pale type predominates. The segregation of the two types of fiber in different muscles is more pronounced in some animals, e.g., the bird, rabbit, than in others. In man and the monkey two kinds of muscle can be distinguished with

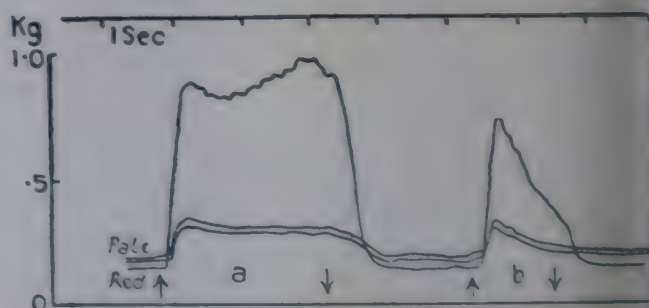


FIG. 342. The reflex effect of the labyrinthine stimulation on neck reflexes on red and pale muscle. Preparation with section of brain-stem slightly anterior to superior colliculi. M. triceps, short lateral head (pale), dashed line; short medial head (red), single line. Labyrinthine stimulation at \uparrow and ventriflexion at \downarrow . Labyrinthine stimulation in each neck posture. Creed, Denny-Brown, Eccles, Liddell and Sherrington, *Reflex Activity of the Spinal Cord*, Cambridge University Press, 1930.

naked eye, though the differences are not so pronounced. The predominance of one type of fiber, can, however, be readily made out with a microscope. The rapidly contracting muscles are largely composed of the pale fibers, while the slowly contracting, pale component is the characteristic of the deep, slowly acting dark head. For example, the gastrocnemius contracts rapidly and contains a large proportion of the pale fibers, while the slowly contracting soleus. The latter is composed of the red fibers and contracts rapidly. The short head of the triceps is pale and contracts rapidly, while the long head is dark and contracts more slowly. The slowly acting deep components of the figure are those which respond most readily to a sudden stimulus, and so show the greatest rigidity. They are the "focus of the stretch reflex" and upon them that labyrinthine and vestibular reflexes are mainly exhibited. The rapidly contracting muscles are more especially concerned with the maintenance of posture.

³ They resemble the intrafusal fibers of the spindle (p. 805).

ements. No hard and fast line, however, exists, since both types of extensor muscle and both take part in phasic contractions.

Action of the sympathetic innervation of skeletal muscle

Apparent dissimilarities between postural or tonic contractions and the rapid contractions resulting from phasic contractions have led some investigators to believe that these two types of muscular activity are fundamentally different. A theory has been put up which postulated two components in muscular activity. A plastic element (plastic tonus) is due to the sarcoplasm of the muscle fiber, and is dependent upon sympathetic innervation and a contractile element (so-called contractile tonus) involving phasic contractions, it was supposed, were dependent solely upon the sarcostyles and somatic innervation. The red muscles, which are rich in sarcomeres and undergo tonic contraction upon somatic and sympathetic innervation. The red muscles contain a large proportion of fibers rich in sarcomeres and were therefore considered to be the "bar excellence." That the red muscles undergo a greater degree than do white muscles, and that there are two types of contraction, one dependent upon the sarcoplasm and under sympathetic innervation, is not generally accepted. Hunter and others carried out experiments upon birds and goats designed to support the theory of the dual nature of muscular activity and sought to apply it to the treatment of certain nervous conditions in man associated with increased tone (spasticity). They sectioned the sympathetic communicantes conveying sympathetic innervation to the affected limb and reported favorable results upon the hypertonic condition. The benefits obtained can be easily explained, however, are questionable in the spastic condition and may be attributed to the release of the limb which constitutes part of the treatment. Upon moving the limb to a new position the muscles undergo alterations in the circulation, a purely psychic effect, rather than upon the muscle fiber of the limb. These reactions are Moreover, the theory upon which the reaction is based is not supported by recent work. The lengthening of the muscle is due to muscular contraction, and is due to muscular contraction, and is due to muscular contraction. The muscle is not the same in nature as the muscle which is contracted. Non-medullated nerve fibers are described by several workers as occurring in muscle fibers in structures other than ordinary motor end plates. These fibers, from their appearance, have been called "grape endings" (*terminaisons en grappes*), and it is reported that these endings are located in a section of the ventral spinal cord between the posterior root ganglia, if the posterior root ganglia are left intact, it was concluded

that they belonged to the sympathetic system. The recent degeneration experiments of Tiegs, however, indicate that the grape endings are terminations of somatic motor nerves. When the hind part of the spinal cord in the snake (python) was destroyed by passing a probe up the vertebral canal after amputation of the tail-tip, the grape endings in the muscle which had received their innervations from this part of the cord disappeared. The postganglionic sympathetic fibers and the posterior root ganglia were of course undisturbed by the operation. Moreover, no sympathetic fibers, other than those supplying the blood vessels, were found in the muscle.

In the light of these histological findings, how is the Orbeli effect to be explained? Orbeli found that the fatigue of a muscle stimulated *through its nerve* (i.e., indirectly) was reduced by concurrent stimulation of sympathetic fibers going to the muscle. Sympathetic stimulation was, however, without effect upon the contractions of a muscle stimulated *directly*. These results lead to the conclusion that the sympathetic effect was exerted upon the motor-end plate. Corkill

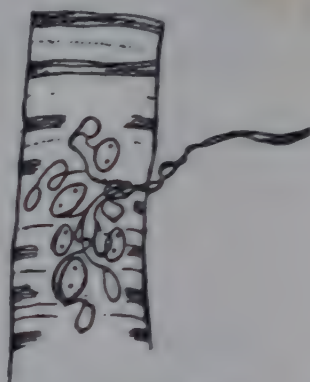


FIG. 343. Diagram showing "grape endings" (*terminaisons en grappes*) upon skeletal muscle.

and Tiegs have recently confirmed Orbeli's observations. Nevertheless, since the muscle fibers themselves are apparently devoid of sympathetic innervation, at any rate none have ever been described as terminating in the motor end plate, the effect, it is suggested, results from the liberation of an adrenaline-like substance (sympathin) from vascular sympathetic endings. (See fig. 344.) The action of adrenaline in postponing muscular fatigue has been mentioned p. 687.

DECEREBRATE RIGIDITY

This is the term applied to the sustained contraction of the extensor muscles which supervenes upon transection of the brain stem at any level between the anterior colliculi and the vestibular nuclei.⁴ The animal assumes a characteristic attitude with limbs stiffly extended, head retracted,

⁴ Decerebration can also be produced by tying the common carotids and the basilar artery at the center of the pons and thereby depriving the fore-brain of its blood supply.

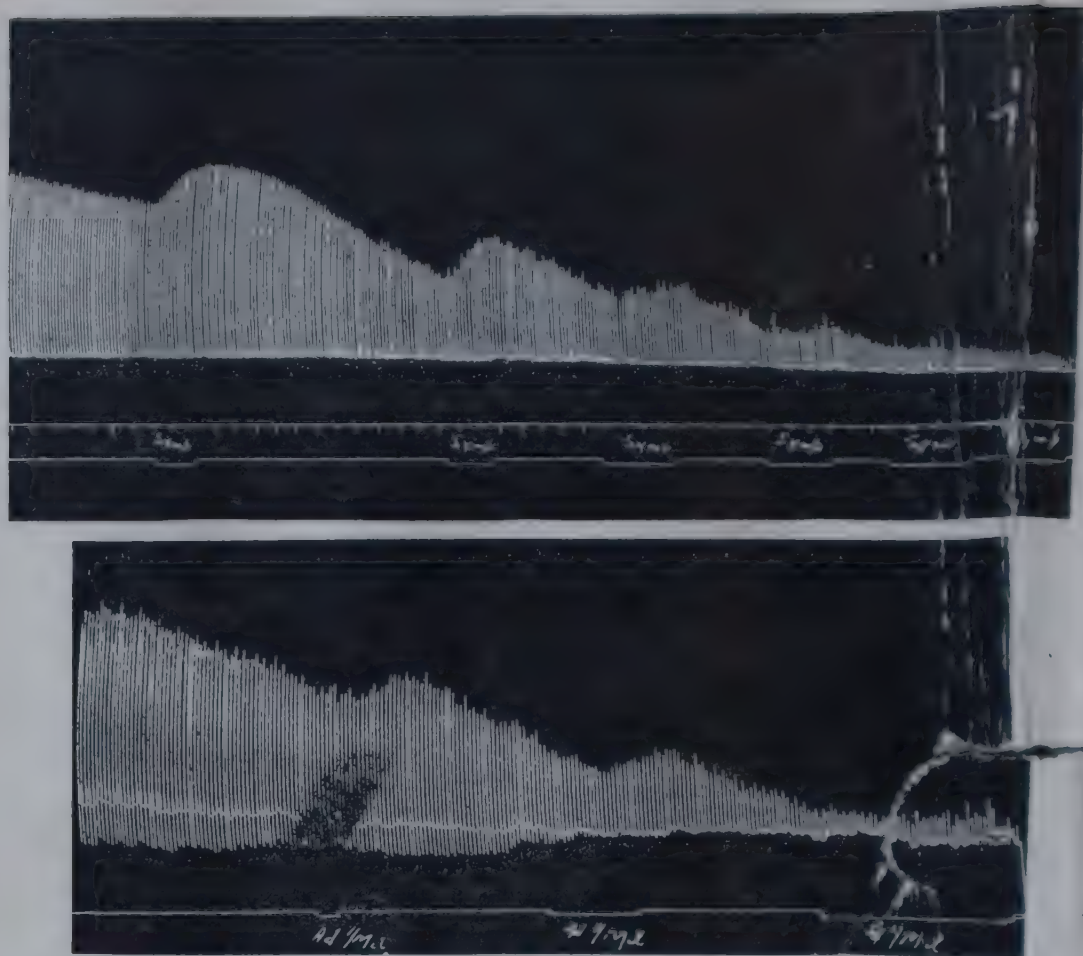


FIG. 344. The effect of sympathetic stimulation (upper tracing) and of adrenaline (lower tracing) on fatigue of skeletal muscle activated through its motor nerve (from Corkill and Tiegs).

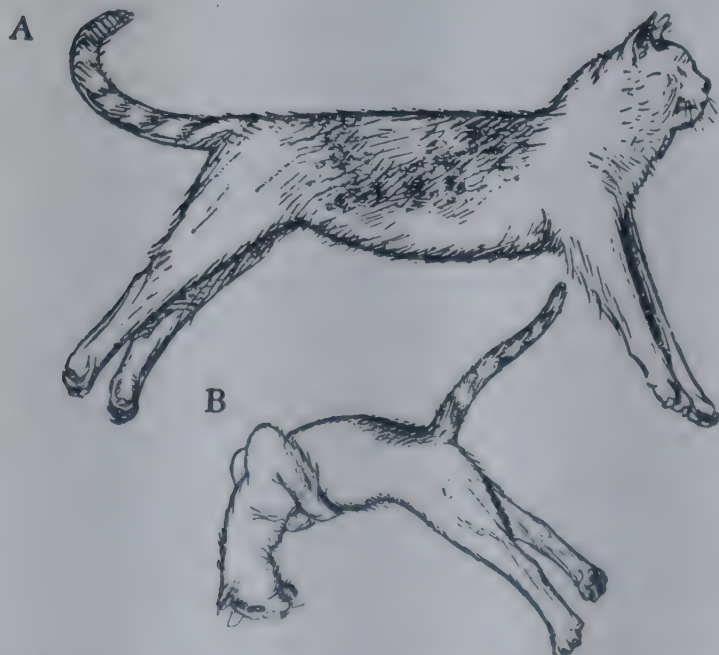


FIG. 345. A suspended decerebrate cat showing extensor rigidity. In A, the labyrinths are intact. B, a decerebrate and labyrinthectomized animal. As a result of the destruction of the labyrinths the head has dropped; this position of the head induces reflex flexion of the fore-limbs and extension of the hind-limbs (tonic neck reflexes, p. 830) (after Pollock and Davis).

jaws closed, and tail horizontal or erect. When placed upon its feet the limbs support the weight of the body (fig. 345A). The position is a caricature of the normal standing position. The knee

jerk and other stretch reflexes (p. 82) generated. The righting reflexes are absent. Neck and labyrinthine reflexes are retained. Ability to regulate the body temperature

In some instances there is increased tonic rigidity as well, but the characteristic feature of rigidity is the tonic contraction of the muscles to maintain the posture. (p. 823, the antigravity muscles). It is pointed out that in the frog which is suspended with flexed thighs, legs and arms, the muscles which are the site of decerebration are the sloth whose habit is to suspend itself from a tree by its arms. The characteristic result of decerebration is basal flexion of the wings which is based on the position of the wing muscles which hold the body in an erect position. In the decerebrate animal the muscles which hold the body in an erect position show increased rigidity. This is decerebrate rigidity which has been described without the muscles in skeletal

The reflex nature of the structures,

Labyrinthine preparation. Little is known of the tone of the neck after decerebration. After destruction of the cerebellum, after preparation the head of the animal falls into the fully extended position.

the forelimbs in turn is maintained through proprioceptive reflexes initiated in the extended neck muscles as well as directly through labyrinthine reflexes (p. 830). After labyrinthectomy, therefore, the flexed position assumed by the head sets up proprioceptive impulses from the neck muscles which lead to a reduction in the extensor tone of the forelimbs; these then become strongly flexed upon the chest (fig. 345 B). If the neck muscles of the labyrinthectomized animal are deafferented, movements of the head are without effect upon the extensor muscles of either fore or hind limbs; deafferentation of the forelimb muscles themselves is followed by little change in the extensor tone of the forelimbs. On the contrary, the extensor rigidity of the hind limbs, is affected relatively little by labyrinthectomy or deafferentation of the neck muscles, but is abolished by deafferentation of the hind limb muscles themselves. To sum up, the tone of the forelimb extensors is maintained chiefly by labyrinthine and neck reflexes, proprioceptive impulses from the forelimb muscles themselves playing a very minor part. In the hind limbs the extensor rigidity is maintained mainly through proprioceptive reflexes initiated from the corresponding limb muscles.

Lengthening and shortening reactions

Attempts at passive flexion of the extended limb of the decerebrate (or chronic spinal) preparation are met by considerable resistance. If the force maintains inhibition of the stretch reflex (upon which the resistance depends) results; the limb gives way suddenly (*clasp-knife effect*) and may now be easily flexed to any degree. The elongation of the extensors which permits the flexion of the limb is called the "*lengthening reaction*." Upon moving the limb again into the extended position the muscle shortens adaptively to the new position. This is the "*shortening reaction*." These reactions give the muscles a certain plasticity. The giving way of the extensor spasm in the lengthening reaction has been ascribed to the giving up of inhibitory proprioceptive impulses to the muscle when the stretch stimulus reaches a certain intensity. As the knee extensor is initiated a contraction of the opposite knee extensor occurs; this is known as Phillipson's reflex.

of the central mechanisms concerned
body temperature of decerebrate rigidity
carrying out coördination
ten to an exaggerated
the intact animal succeeded in keeping ani-
two to three weeks after
ates (fright, anger). the mid-brain. The ani-

mals showed extensor rigidity up to the day of death, though as time elapsed the condition tended to be less constant, intervals of reduced extensor and increased flexor tone alternating with those showing the typical decerebrate posture. The fact that extensor rigidity was present so long after operation makes it clear that the condition is not due to the irritation of fibers at the line of section, for these must have undergone degeneration before the end of the survival period. Decerebrate rigidity is evidently due to the release from higher control of a center or centers situated below the level of the transection. The rigidity persists after removal of the cerebellum (cerebellar stimulation actually inhibits the extensor rigidity) but is abolished by destruction of the vestibular nuclei or of the vestibulospinal tracts. The vestibular nuclei or structures in their immediate vicinity therefore appear to be the centers mainly responsible for decerebrate rigidity.

Some of the pseudoaffective reactions characteristic of the thalamic or decorticate animal (p. 884) are seen in the decerebrate preparation to a minor degree. Bazett and Penfield record that in their chronic decerebrate animals stimulation of the preparation, as by twisting the ear, caused lashing of the tail; kicking and running movements were induced by merely touching the animal. Purring followed the introduction of milk into the stomach. Other reflexes whose centers are apparently located in the medulla consisted of motions of chewing and swallowing upon the passage of a stomach tube, and licking movements upon its removal; growling, mewling or crying also occurred in response to various types of stimulus. Auditory reflexes, consisting of movements of the head, limbs or tail, in response to certain sounds, especially to a small scratching sound resembling that made by a mouse were also observed.

The origin of the influence from which the lower centers are released by decerebration is not definitely known. According to Rademaker the red nucleus is responsible for the normal distribution of tone. He reported that transection of the brain anterior to the red nucleus did not result in extensor rigidity, whereas the latter followed immediately upon the destruction of the red nucleus itself, or section of the rubrospinal tracts at the decussation of Forel. These findings are not, however, in accord with those of other workers, and the view that the red nucleus bears an essential relationship to the development of extensor rigidity is no longer generally accepted.
Bazett et al.

rigidity was produced by division of the anterior part of the mid-brain which apparently differed in no respect from that resulting from transection behind the red nuclei. Kellar and Hare, and Ranson and his associates also found that lesions which completely destroyed, but were restricted to, the red nuclei caused an increase in extensor tone which was quite mild as compared with that characteristic of the decerebrate preparation.

The thalamic animal shows a nearly normal distribution of tone but, as just mentioned, well marked extensor rigidity ensues upon section of the brain through the anterior part of the mid-brain, i.e., at about the level of the posterior part of the thalamus. These facts point to the diencephalon (possibly the hypothalamus) as the origin of the tracts whose division causes the abnormal tonus distribution. Yet the thalamic or decorticated animal does show some tendency towards extensor rigidity (p. 829) which indicates that the cerebral cortex also plays a part in regulating the activity of the lower tonic centers. It is probable therefore that for the full development of decerebrate rigidity the removal of both cortical and diencephalic influences is required. The question whether the cortical influence emanates from the motor or premotor cortex has not been definitely settled (see p. 890). According to Elliott Smith and Abbie the frontopontine tracts, which descend from the premotor cortex through the mid-brain to the pons, convey impulses which normally serve to release the limb muscles from the rigidity of the standing posture. Section of these tracts or ablation of the premotor cortex would therefore "fix" the muscles and maintain the rigidly extended posture of the limbs which is characteristic of decerebrate preparations. This conception is in harmony with the results of cortical extirpations in the chimpanzee.

Decerebrate rigidity in man

States of hypertonus resembling decerebrate rigidity are seen in certain nervous diseases. The spasticity of the hemiplegic limbs, for example, has been compared with the experimental condition, but the hypertonus is, as a rule, much less pronounced in the hemiplegic patient than in the decerebrate animal. Moreover, in hemiplegia, though the lower limbs are extended, in the arm it is the flexor muscles which are hypertonic. It may be mentioned, however, in this connection that in the ape standing upon its hind limbs the flexors of the forelimbs are the postural muscles and hold the limbs in a semiflexed position.

gravity; it is these muscles, as already mentioned, which show rigidity after decerebration. When on the other hand, the animal goes upon all fours the extensor as well as the flexor muscles become hypertonic like those of lower mammals and convert the limbs into rigid supports for the body. It has been shown by Brain that when the hemiplegic patient assumes the quadrupedal position the rigidity also shifts from the flexors of the arm to the extensors; the arm is extended and offers resistance to passive flexion. This suggests that the ordinary flexed position of the hemiplegic arm is in reality, as in the decerebrate ape, a part reflex bipedal standing. Whether the spasticity of hemiplegia is due to pyramidal or extra-pyramidal involvement has been a debatable question, but it is most likely the result of injury to the lateral system (p. 890).

Rigidity is a pronounced feature of striatal disease but it differs from decerebrate rigidity in that the flexors as well as the extensors are hypertonic.

A posture which is most closely comparable with decerebrate rigidity is seen in association with hydrocephalus or lesions of the mid-brain. In such cases the four limbs are rigidly extended. Such lesions tend to cause extensive destruction of nervous tissue which further supports the view that the full development of decerebrate rigidity is due to the interruption of more than one descending pathway.

THE SPINAL STATE

Transection of the cord produces an immediate flaccid paralysis of the muscles behind the point of section. Immediately after section in the lower cervical region the limbs hang limply, the extensors being quite toneless; the stretch reflexes and other extensor responses cannot be elicited; the startle jerk is abolished. The blood pressure falls to a dangerously low level and vascular and visceromotor reflexes are unobtainable. This condition is called *spinal shock*. Its duration varies with the species. The higher the position of the lesion in the phylogenetic scale the more profound is the shock and the slower is the recovery. In the frog the condition is brief; in the rabbit, cat and dog the startle jerk returns within a few minutes, but in the monkey not for two or three days. Other extensor reflexes, however, remain in abeyance for a longer time. In the cat and dog the startle reflex is still present after a long time. In the cat and dog the startle reflex is still present after a long time. In the cat and dog the startle reflex is still present after a long time.

decerebrate preparation is sectioned, the exaggerated extensor tone characteristic of the latter is replaced (behind the section) by an imbalance in favor of the flexor muscles.

Spinal shock also follows section through the medulla below the vestibular nuclei (*decapitate preparation*).

In the cat and dog spinal shock is gradually covered from over a period of weeks. The blood pressure is restored to normal and the vascular reflexes can again be obtained. The reactions of the extensor muscles return, and the animal is able, though imperfectly and for a few minutes only, to support the weight of the body when placed upon its feet (chronic spinal animal).

Spinal shock is attributed to the removal of impulses which in the intact animal descend from higher centers to reinforce the spinal centers. That it is due to this and not simply to an inhibitory effect of the local injury itself seems clear from the fact that after an animal has recovered from spinal shock, a second transection made behind the original one does not cause a return of the shock state. In the cat and dog the flexor reflexes are evidently dependent only to a minor extent upon the higher centers, since they are capable of being executed by the spinal centers alone. The loss of the extensor reactions results from the removal of vestibular impulses (severance of vestibulospinal tracts) but these reactions can also eventually be carried out by the spinal centers. In the monkey, the immediate effect of cord section upon reflex activity is much more profound, involving the flexors as well as the extensors. The loss of the flexor reactions is probably due to the greater dependence of the flexor spinal centers of this species upon impulse arriving by descending pathways (reticulospinal). Ultimate recovery of reflex activity in the monkey is slight; any which results is confined to the flexors and the knee jerk. The muscles waste and the limbs remain flaccid. The failure of recovery eventually to occur is probably due to degeneration of anterior horn cells below the level of the cord section (atrophy), the long duration of the shocked state permitting the cells to deteriorate beyond the time within which repair is possible (see also p. 871).

THE THALAMIC ANIMAL

This term is given to an animal whose cerebral hemispheres have been removed, leaving the optic thalami intact (see fig. 349). Such preparations retain their righting reflexes and can regulate their body temperature. They are also capable of carrying out coördinated reflex acts and show, even to an exaggerated degree, reactions which in the intact animal are associated with emotional states (fright, anger). Such reactions, which are

termed pseudoaffective, are also exhibited by an animal whose cortex alone has been ablated (see p. 884). In contrast to the decerebrate animal, the distribution of muscular tone in the thalamic animal shows little departure from the normal, though a tendency toward extensor rigidity is evident when the animal is held suspended in mid-air.

STATIC AND STATO-KINETIC REFLEXES

The reflex mechanisms governing the orientation of the head in space, the position of the head in relation to the trunk and the appropriate adjustments of limbs and eyes to the position of the head, are called into action by afferent impulses discharged from receptors situated in (a) the vestibular apparatus (semicircular canals or utricle), (b) the neck muscles, (c) the retina, and (d) in the body wall or limb muscles.

The postural reflexes are classed into two main groups, *static* and *statokinetic*.

(1) *Static reflexes*. These are *general* and *local* or *segmental*. The general static reactions, so called by Magnus because they involve the entire body, or at least four limbs, are (a) the *righting reactions* and (b) the *statotonic* reflexes. The general static reactions are called into play by the deviation of the head from its usual or "natural" position in space (stimulation of receptors of utricle, p. 835) or in relation to the trunk (stimulation of neck muscle receptors). The local or segmental static reactions are confined to one limb or a pair of limbs; examples are, the *supporting reactions* and the *crossed extension reflex*. The latter reflex has been described on page 819.

(2) *Stato-kinetic reflexes*. The actual *movements* of the head bring these reflexes into action (stimulation of receptors in semicircular canals).

When an animal's head moves in space as a result of a movement of the neck, or of a change in the position of the body as a whole, the reflex adjustments of limbs and eyes which accompany a particular movement of the head are brought about through stato-kinetic reactions. The attitude which is thus struck is sustained by a statotonic reflex so long as the head is in the new position. The righting reflexes serve to maintain the normal upright position of the body or to restore this position if as a result of some untoward movement or the application of an external force the animal is thrown upon its side or back. A more detailed account of these different postural reflexes follows.

GENERAL STATIC REFLEXES

THE RIGHTING REFLEXES

The orientation of the head in space is a faculty possessed by all vertebrates and by many invertebrates, and the ability to maintain the head in a definite relationship to the body is a general characteristic of animal life. A cat held back downwards and then allowed to fall through the air lands upon its feet, its body and head assuming a normal attitude. A fish resists any attempt to turn it from its natural position and if placed in the water upon its back flips almost instantly into the normal swimming position. Even a cray-fish rights itself from the back-down position. These righting reactions are complex and involve five separate types of reflex.



FIG. 346. On left, position taken up by a thalamic rabbit with intact labyrinths. As it possesses the labyrinthine righting reflexes, it carries its head in the normal position. On right, position taken up by a rabbit like the preceding but deprived of its labyrinths. The head is not raised towards the normal position (after Magnus).

(a) Labyrinthine righting reflexes acting upon the neck muscles.

(b) Neck righting reflexes acting upon the body.

(c) Body righting reflexes acting upon the head.

(d) Body righting reflexes acting upon the body.

(e) Optical righting reflexes.

The first four of these are demonstrated best upon a thalamic animal (p. 829). When a thalamic rabbit is suspended from the pelvis (fig. 346) the head turns until it assumes its normal position in space, i.e., into the position it would occupy were the animal in its natural position. The maintenance of the head in the new position is due to *labyrinthine righting reflexes* acting upon the neck muscles. Turning the body of the animal through the air into different positions is followed by compensatory movements of the head, its orientation

in space being thereby maintained. A pation of the labyrinths and suspended animal as before, the head shows no compensatory movements; it hangs limply like that of a rabbit.

When the thalamic animal is laid rest its side on a table the head is raised into upright position as a result of the *labyrinthine righting reflexes* just mentioned. The contractile neck muscles which rotate the head sets up proprioceptive impulses, which through the upper cervical cord exert an influence upon the muscles of the body which rotate (first, then pelvis) into the normal relationship to the head. This is the *neck righting reflex acting upon the body*. A labyrinthectomized animal laid upon its side behaves in a somewhat abnormal manner. The reaction under the latter stances is due, however, to the asymmetrical stimulation (pressure of one side of the body against the table) of exteroceptors in the body wall. This is the *body righting reflex acting upon the head*. If a board of a weight equal to that of the animal is laid upon its upper surface, the pressure is thereby disposed equally on the two sides and no compensatory movement of the head occurs.

This reflex is well shown by the labyrinthine dogfish, especially after blinding. When placed upon its side or back the fish despite the absence of labyrinths swims away in the false position. However, it comes into contact with the bottom of the tank the righting reaction immediately occurs. Even worms possess this means of orientation.

Again, when the thalamic animal is laid upon its side but the head held down to the table to eliminate the righting reflexes of labyrinthine and cervical origin, as well as the body righting reflex acting upon the head, the body nevertheless rights itself. This must be due to the asymmetrical pressure upon the body exerting a reaction upon the skeletal musculature, i.e., a *body righting reflex acting upon the body*.

The *optical righting reflexes* are initiated by retinal impressions. They are absent in the thalamic animal since their center is cortical. In many animals, such as the monkey, dog and cat but are a negligible factor in others, such as the rabbit and guinea pig. The absence of the optical righting reflexes in the thalamic species is attributed to their lower cortical development. Yet even the cray-fish deprived

which is the homologue of the utricle of the ear, rights itself, though with less facility usually, when placed upside down in water. Medium righting reflexes due to unequally distributed pressures upon the body surface must also be in abeyance; the righting reaction, apparently entirely of retinal origin. This is so is proved by blinding the animal, in which case the righting reaction is lost completely.

In sum, the righting reflexes may now be studied in their natural sequence. When the animal is placed upon its back the labyrinthine reflex upon the neck muscles turns the head into a normal relationship to the dimensions of space; the proprioceptive reflexes of the neck muscles bring the body into its normal relation to the head. When resting upon a rigid support these reflexes are reinforced by body righting reflexes (head and body). When the animal falls through the air or water, the latter reflexes of course come into play. A labyrinthectomized otherwise normal animal, such as the cat or guinea pig, covers its upright position when allowed to fall through the air, as a result of the operation of the righting reactions; the righting ability is, however, if the eyes are covered with a black cloth. Also, an air-breathing animal deprived of both labyrinths, though a good swimmer, drowns if thrown into deep water, since it cannot orient itself with respect to the sight of surrounding objects. Deaf mutes, guinea pigs, whose labyrinths are very frequently undeveloped, are unable to swim and may drown as a result of their inability to orient themselves when diving into deep water.

Righting reflexes may be demonstrated in the guinea pig. The baby of a few weeks old, for example, when lying prone raises the head into a vertical position. When blindfolded and held by the pelvis in different positions in the air the head is moved toward the normal position.

ATONIC OR ATTITUDINAL REFLEXES

Tonic labyrinthine and neck reflexes acting on the limbs. These reflexes influence the tone of the skeletal muscles and thereby maintain the different parts of the body in an attitude appropriate to a given position of the head. They are investigated best in the decerebrate animal (fig. 347), the righting reflexes being then largely excluded. The proprioceptors concerned are in the labyrinth (tonic labyrinthine (utricle) reflexes) which are brought into play by alterations in the position of the head in relation to the dimensions of space, (b) the neck muscles (tonic

neck reflexes) which come into action when the position of the head is altered relatively to the body. In order to study separately the part played by each of these reflexes in any given reaction, the following procedures are adopted.

A. To exclude the neck reflexes:

(a) Immobilization of the neck of an animal by means of a plaster of Paris bandage in order to prevent movement of the head in relation to the trunk. Any tonic effects resulting from a change in the animal's position must then be due solely to alterations in the position of the head in space (labyrinthine reflexes).

(b) Section of the posterior roots of the first three or four pairs of cervical nerves.

B. To exclude tonic labyrinthine reflexes:

(a) Fixation of the head alone in some suitable apparatus. The tonic effects resulting from movement

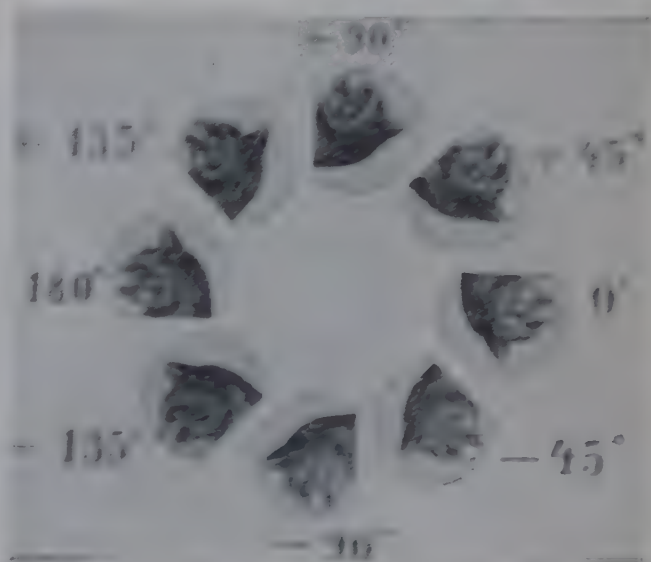


FIG. 347. Diagrammatic representation of the positions of an animal's head, each marked with the angle which the labial cleft makes with the horizontal plane (after Magnus).

of the body must then be due to an alteration in the position of the body in relation to the head, i.e., to movements of the neck.

(b) Destruction of both labyrinths, section of the 8th nerves or of the medulla below the vestibular nuclei.

The labyrinthine reflexes exert an influence upon the tone of the extensor muscles which is in the same direction (increase or decrease) in all four limbs. The influence of the neck reflexes, on the other hand, is usually in opposite directions in the fore and hind pairs of limbs. The greatest degree of extensor tone is exerted through the labyrinth mechanism when the animal is supine and the mouth cleft inclined at an angle of 45° (fig. 347) above the horizontal plane.

Extensor tone diminishes as the angle increases; it is minimal in the prone position with the mouth cleft at an angle of 45° below the horizontal plane.

In an animal on all fours the labyrinthine effect is therefore to increase or decrease the extensor tone in the muscles of all four limbs when the head is strongly extended or flexed, respectively. In the decerebrate labyrinthectomized animal, the neck reflexes alone operating, flexion of the forelimbs and extension of the hind limbs occur when the neck is flexed toward the sternum (ventriflexion), (see fig. 345, p. 826). Extension of the neck (dorsiflexion) produces the converse picture, i.e., extension of the forelimbs and flexion of the hind limbs. When therefore the neck is ventriflexed in the decerebrate animal with intact labyrinths, the neck reflexes reinforce the tonic labyrinthine effect upon the forelimbs but antagonize that upon the hind limbs; the usual result is relaxation of the forelimbs with strong extension of the hind limbs. When the neck is extended the

a corner is accompanied by similar effects—extension of the limbs on the side of the body toward which the jaw (or snout) is inclined (*jaw limbs*) and flexion of the limbs on the opposite side (*skull limbs*).

Pressure upon the last cervical vertebra reduces the tone in all four limbs (*vertebra prominens reflex*).

The significance of these reflexes and their importance in the coordination of the postural muscles may be realized when the attitudes of the intact animal are observed. Thus when an animal turns to one side the limbs of that side are stiffened in order to support the body's weight. A cat looking upwards to a bird in a tree extends the forelimbs and flexes the hind limbs, thus giving the back a suitable inclination which improves the position of the head and eyes, and places the body



FIG. 348. Photographs of a normal cat, showing the animal's posture (on left) when its attention is attracted by an object placed above it. Photograph of the same animal (on right) when its attention is drawn to an object below it. The difference between the two positions of the forelimbs is very marked, because in them the neck and labyrinthine reflexes reinforce one another; the hindlimbs are in much the same position in both cases since the two sets of reflexes cancel one another (after Magnus).

neck reflexes reinforce the labyrinthine effect upon the tone of the fore limbs but antagonize that upon the hind limbs. The effect of the neck reflexes upon the extensor tone of the latter again predominates; the extension of the forelimbs is maintained but definite relaxation of the hind limbs occurs.

Rotation of an animal's head (turning in the frontal plane of the skull) causes increased extensor tone of the fore and hind limbs on the side of the body toward which the jaw is rotated (*jaw limbs*)⁵ and reduces the tone of the opposite limbs (*skull limbs*). Inclination of the head toward one shoulder (lateral flexion) as when an animal turns

in a position preparatory for a spring (fig. 348). When looking into a hole or beneath a cupboard the flexion of the forelimbs and extension of the hind quarters gives an opposite but no less advantageous inclination to the body. Depression of the back in the region of the last cervical vertebra brings the animal into a crouching attitude.

Stato-tonic effects may be demonstrated in certain nervous lesions associated with a state analogous to decerebrate rigidity of animals (p. 825). Turning the head to one side, for example, causes an increase in tone of the extensors of the jaw limbs and hypotonicity in the limb muscles of the opposite side).⁶ When the head is in the position for maximal labyrinthine tone, i.e., when the

⁵ Magnus has introduced the term jaw-limbs to indicate the limbs toward which the chin of man or the jaw of animals is rotated or inclined. The opposite limbs i.e., the limbs to which the vertex of the skull is rotated, are called skull-limbs.

⁶ This, according to Magnus, can also be shown in a certain percentage of normal infants, and in hydrocephalus it may be well marked.

patient is supine, and the neck extended the extensor tone of the paralyzed limbs increases, but becomes reduced in the prone position.

(2) *Tonic labyrinthine and cervical reflexes acting upon the eyes.* Tonic effects upon the eye muscles, analogous to those described for the skeletal muscles, result from changes in the position of the head. Labyrinthine and neck reflexes are responsible. Alteration in the position of the head with neck immobilized, or movement of the head in relation to the body after labyrinthectomy, is followed by compensatory eye movements. Turning the head downwards causes an upward movement of the eyes which are held in this position so long as the head position is maintained, the tone of the superior recti and inferior oblique being increased while that of the inferior recti and superior oblique is reduced. A corresponding compensatory movement of the eyes occurs when the head is turned upward. Similarly, when the head is turned to one side the internal and external recti of the two eyes cooperate to deviate the eyes outward or inward in relation to the head. Briefly, the eyes are moved in a direction opposite to that taken by the head; thus their original positions in space are maintained and the visual field existing prior to the head movement remains unaltered. It should be pointed out that the actual movement of the eyes is a stato-kinetic reflex (p. 834) and due to a different mechanism (semicircular canals) from that which maintains the eye position while the head is held in the altered attitude. The latter is a statotonic reflex, dependent upon the utricle.

SUMMARY OF THE CENTERS FOR GENERAL STATIC REFLEXES

Magnus found that all the static reactions mentioned in the foregoing section could be obtained unaltered after removal of the cerebellum, as could also most of the stato-kinetic reflexes to be described in the next section. Nevertheless, this rather surprising fact does not necessarily imply that in the normal intact animal the cerebellum plays no part in these reactions. A contrary conclusion must be drawn from anatomical considerations and from observations in cerebellar disease in which disturbances referable to the labyrinth (e.g., abnormal positions of head, falling, etc.) are manifest. Moreover, Camis has demonstrated the arrival of action currents in the cerebellar nuclei during experimental stimulation (mechanical) of the labyrinth.

(a) *The righting reflexes.* All the labyrinthine righting reflexes, as well as the body righting reflexes acting upon the head, have their centers in the mid-brain. According to Rademaker the labyrinthine righting reflexes are dependent upon the red nucleus. Destruction of the red nuclei or section of the decussation of Forel (p. 875) is claimed by this observer to abolish the righting reflexes.⁷ The center for the optical righting reflexes is cortical, that for the body righting reflexes acting upon the head have their centers in the neighborhood of but not in the red nucleus itself (Magnus).

(b) *The stato-tonic labyrinthine reflexes* acting upon the skeletal muscles have the center in the vestibular nuclei.

(c) *The neck reflexes* are centered in the upper two or three cervical segments of the cord (see fig. 349).

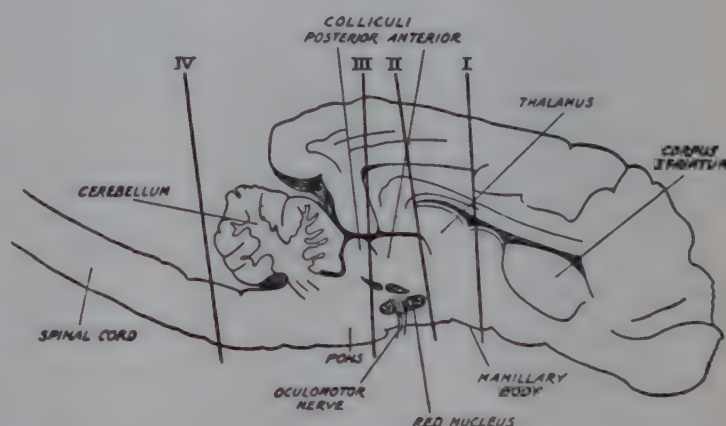


FIG. 349. Diagram to illustrate the effects of sections through cat's brain at various levels. Line I, thalamic animal, righting, tonic labyrinthine and neck reflexes retained; little disturbance of muscular tone; Lines II and III, decerebrate rigidity; Line IV, behind vestibular nucleus, decapitate animal, extensor rigidity abolished, tonic neck reflexes retained. Section at level of second or third cervical segment of the cord—spinal animal—abolishes the tonic neck reflexes (after Magnus).

(d) The centers for the *tonic labyrinthine and cervical reflexes acting upon the eyes* are situated between the vestibular nuclei and the nuclei of the nerves to the eye muscles.

LOCAL STATIC REACTIONS. SUPPORTING REACTIONS

Magnus speaks of the simultaneous reflex contractions of extensor and flexor muscles and other opposing muscles whereby the joints are fixed and the limbs converted into rigid pillars for the support of the body against gravity as the *positive*

⁷ The conclusion that the red nucleus is the essential center for the labyrinthine righting reflexes has been recently contested. Keller and Hare found that sectioning the rubrospinal tracts did not abolish them. (See also, Ranson and associates.)

supporting reaction. This reaction is initiated by:—

(a) Impulses discharged from the proprioceptors of the flexor muscles of the terminal segments of the limbs—digits and ankle or wrist; the pressure of an animal's paw upon the ground by stretching these muscles provides the adequate stimulus which calls forth simultaneous reflex contractions of the flexors and extensors of the knee (or elbow).

(b) Myotatic reflexes set up in the flexors of ankle and toes (plantar flexors) or of the terminal joints of the forelimb; excessive extension at these joints is thus counteracted. Any tendency toward over-extension at the knee or elbow is also provided against through the reflex set up when the flexors of these joints are stretched. Similarly, any tendency of the knee or elbow to bend under the weight of the body calls forth a myotatic reflex from the extensors, which prevents any weakening of the supporting action of the limb.

(c) Impulses set up in the pressure receptors in the deeper layers of the skin of the sole when in contact with the ground; thus exteroceptive reflexes reinforce those of proprioceptive origin. The exteroceptor element is well shown in a decerebellated dog. When such a preparation is placed upon its back and the head strongly flexed, the hind limbs are flexed in all joints. Light pressure with the finger upon the toe pad then causes an extension of the limb, and if the finger be moved with the limb as it extends so that only very light pressure upon the pad is maintained, one has the sensation of the limb being drawn out by the finger. For this reason the movement has been called the "magnet reaction."

The relaxation of the muscles and the unfixing of the joints which enables the limb to be flexed and moved to a new position is called the *negative supporting reaction*. It is brought about by raising the pad off the ground and plantar flexing the toes and ankle. The exteroceptive stimulus and the stretch stimulus to the *plantar flexors* are thus removed. The reflex "unlocking" of the limb is not, however, simply due to the removal of these stimuli, but has in addition a positive element, namely, the stimulus provided by the stretching of the dorsi-flexors of the toes and ankle—relaxation of the extensors of the knee or elbow and contraction of the flexors result.

The supporting reactions, though seen best in a decerebellate animal, can also be demonstrated in the decorticate preparation or in one whose brain-stem has been divided above the medulla oblongata. Segmental static reactions, e.g., flexion

reflex and the crossed extension reflex have been described in Chapter LXV.

Placing and hopping reactions. These were first studied by Rademaker and have been more recently investigated by Bard. Bard and Brooks describe five *placing reactions*.

(1) If a cat is held in mid-air with legs dependent and chin held up so that it cannot see anything below or in front, contact of the backs of the forepaws with the table's edge is followed by a quick movement of the limbs which brings the paws, soles down, precisely upon the surface of the table. (2) If the forelimbs of a cat are held down while the chin is brought in contact with the table near its edge, the forepaws when released are instantly raised and placed upon the table beside the chin, a movement which is usually accompanied by extension of the limbs and the assumption of a standing position. (3) If the fore- or hindlimbs of a cat standing or sitting upon a table are pushed over the table's edge, they are immediately lifted and placed in their original positions. (4) If one abducts, without holding, the limb of a standing cat, it is instantly returned to its previous position. (5) If a blind-folded cat is suspended in the air with forelimbs free, and its head brought toward some obstacle, at the instant that the vibrissae come into contact with the object, the forepaws are raised and accurately planted upon its surface. The first three of these reactions are due to stimulation of receptors upon the body surface (exteroceptors) and probably also of proprioceptors in muscles and tendons. The fourth is a purely proprioceptive reflex; the last is initiated from tactile receptors. The *hopping reactions* consist of limb movements which serve to maintain the standing position against any force acting upon it in a horizontal plane. When, for example, a cat is held so that its body is supported upon one fore- or hindlimb and is then pushed in one or other direction, the supporting limb hops quickly in the direction of the displacement, the foot being kept directly under the corresponding shoulder or hip. The hopping reactions are probably dependent upon myotatic (stretch) reflexes (p. 822).

The placing and hopping reactions are controlled from the sensorimotor area of the cerebral cortex. Removal of this region by Bard and Brooks on both sides was found to abolish the placing reactions, and to produce an extreme degree of deficiency in the hopping reactions. Decortication (complete removal of the neocortex) produced no greater deficiency. The control exerted by the cerebral cortex is entirely contralateral, i.e., the component movements of the reactions on one side of the body are governed solely by the opposite side of the brain.

STATO-KINETIC REFLEXES

ANATOMY OF THE LABYRINTH

Before a description of other labyrinthine functions, e.g., the stato-kinetic reflexes, can be undertaken, a

brief description of the structure of the labyrinth must be given. This structure consists of an auditory (cochlear) and a non-auditory portion. We are concerned here only with the latter which we shall refer to simply as the labyrinth. The *bony labyrinth* comprises a series of cavities tunnelled in the petrous part of the temporal bone. The cavities are the three semicircular canals, each of which opens by its two extremities into an ovoid chamber known as the *vestibule*. The bony labyrinth lodges a series of hollow membranous structures—the *membranous labyrinth*. The membranous labyrinth consists of: (a) *Three semicircular canals* lying in the corresponding bony canals. (b) Two sacs, the *utricle* and *sacculle* situated in the vestibule.

THE SEMICIRCULAR CANALS. One extremity of each canal shows an expansion known as the *ampulla* wherein is situated the specific sense organ. The membranous labyrinth is filled with fluid—the *endo-*

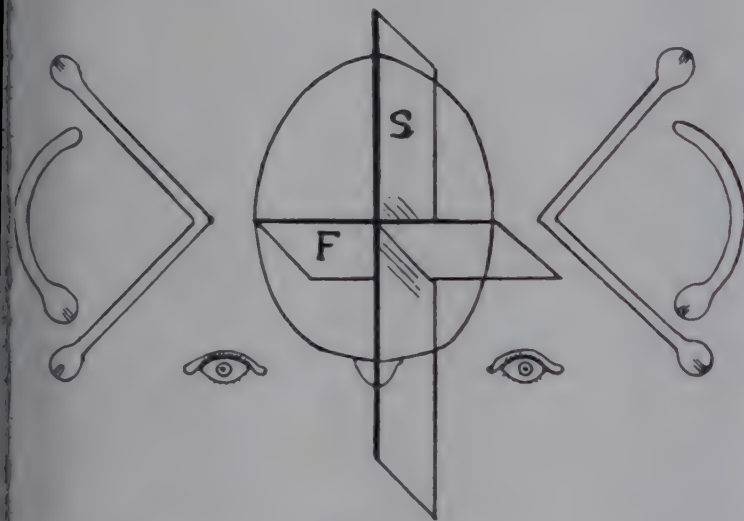


FIG 350. Diagram showing the semicircular canals and their relation to the planes of the skull. S, sagittal plane; F, frontal plane (see text).

lymph: a similar fluid—the *perilymph*—lies between its walls and the walls of the bony labyrinth. The canals lie in planes approximately at right angles to one another and are called respectively *external* (horizontal), *anterior* (vertical) and *posterior* (vertical) (see fig. 350). It will be noted that the non-expanded extremities of the vertical canals join to form a common stem through which they communicate with the utricle (fig. 352).

The external canal is directed with its convexity outwards and backwards. When the head is in the erect position this canal is only approximately horizontal; it is inclined backwards and downwards at an angle of about 30° to the horizontal plane. The vertical (anterior and posterior) canals both make an angle of 45° with the frontal and the sagittal planes of the skull.⁸ The anterior canal of one ear is therefore in the same plane as the posterior canal of the other ear,

⁸ That is, their planes cross both the frontal and sagittal planes diagonally.

whereas the posterior or anterior canal of one ear is at right angles to its fellow of the opposite side as well as to the other two canals of the same ear. The external (horizontal) canals of the two sides lie in the same plane.

THE CRISTA. This is the receptor organ of the semicircular canal. It is situated in the ampulla and



FIG. 351. Cardboard model with the skull of a monkey, to show the planes of the utricle and saccule with respect to the skull (from Camis after de Burlet and Haas).

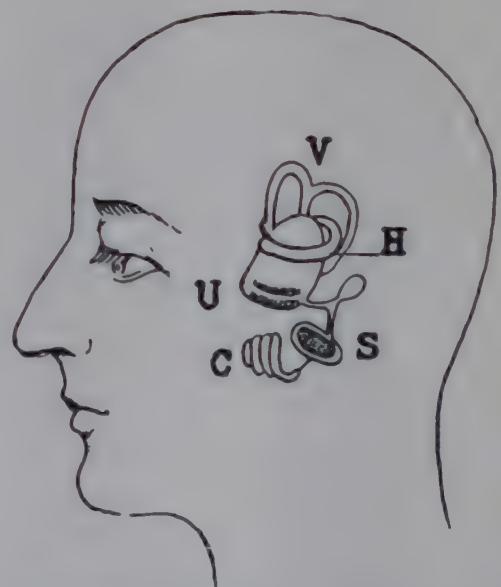


FIG. 352. Diagram (not to scale) giving a lateral view of the internal ear within the skull. V, vertical canals; H, horizontal canal; U, utricle; S, sacculle; C, cochlea (redrawn from Quix).

consists of a mound of sensory hair cells between which are non-sensory supporting cells. The sensory cells are surmounted by a gelatinous dome-shaped structure—the *cupola*; this contains fine longitudinal channels in which the hairs or cilia are lodged.

THE OTOLITH ORGANS—THE UTRICLE AND SACCULE. In the wall of the *utricle* lie the openings of the semicircular canals. It also communicates with the sacculle by a small canal—the *ductus endolymphaticus*. The sense organ of the utricle is called the *macula*. This

consists of a plaque of sensitive hair cells covered by a layer of gelatinous material (otolith membrane) upon which are situated crystals or small concretions of lime—the *otoliths*. The *saccul*e communicates with the utricle on the one hand and with the cochlea on the other. Its communication with the latter is through the duct of Henson. The sense organ of the saccul is also given the name of *macula*^o and is constructed upon a plan similar to that of the utricle. The macula

are in the same plane, whereas the *saccular macula* are in different planes, forming an angle opening forwards and downwards (figs. 351 and 352).

THE NERVOUS CONNECTIONS OF THE LABYRINTH

The impulses from the proprioceptors of the different parts of the non-auditory labyrinth are conveyed to the medulla by the vestibular branch of the 8th nerve

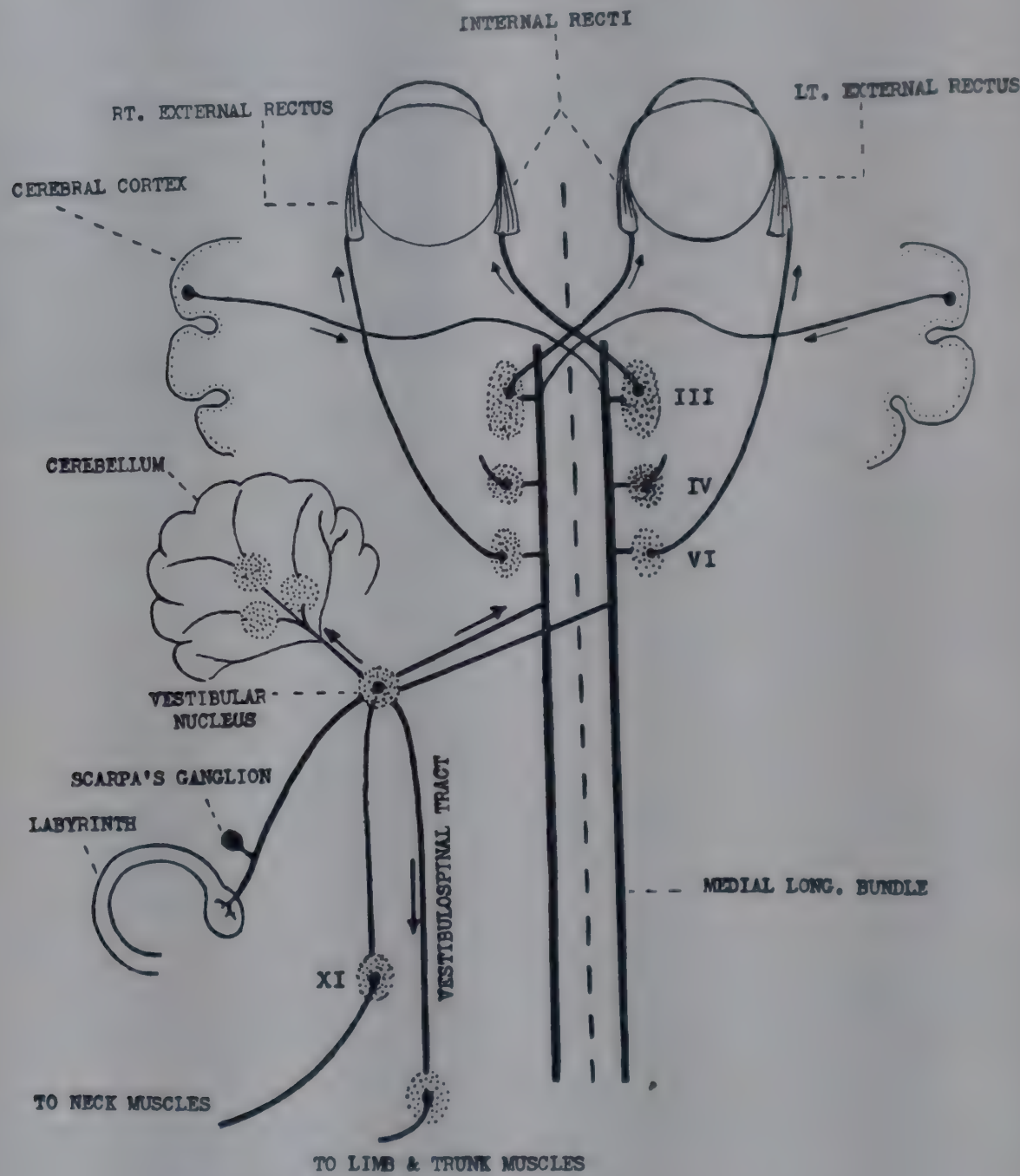


FIG. 353. Diagram of vestibular pathways (see text).

of the utricle is approximately horizontal, sloping slightly downwards and backwards, its front part being curved upwards like the prow of a boat. The saccular macula is roughly vertical, sloping from behind forwards and outwards and from below upwards and inwards. The utricular maculae of the two ears

^oThe term "lapillus" is sometimes applied to the otolithic organ of the utricle while that of the saccul is spoken of as the "sagitta."

The cell bodies of the vestibular fibers lie in Scarpa's ganglion. They pass for the most part to the *vestibular nuclei* in the medulla from which relay fibers follow three pathways (fig. 353). Thus there are:

- (a) Ascending fibers which join the medial longitudinal bundle of the same and opposite sides and pass to the nuclei of the 3rd, 4th and 6th cranial nerves (vestibulo-ocular tract). Through these connections reflex movements of the eyes are brought about.

(b) Descending fibers, constituting the vestibulo-spinal tract, connect with the spinal motor neurons. Through these connections impulses are conveyed to the skeletal muscles.

(c) Fibers which pass to the cerebellar nuclei (N. globosus, emboliformis and fastigii) via the inferior cerebellar peduncle and thence to the cerebellar cortex. These constitute the vestibulo-cerebellar tract. Impulses conveyed along this pathway and thence through the superior cerebellar peduncle to the cerebrum give rise to the sensation of vertigo.

As a result of his clinical findings I. H. Jones concludes that the fibers from the vertical and from the horizontal canals follow different paths. Those from the vertical canals do not according to this observer, enter the vestibular nuclei but ascend to the pons where they divide into two diverging paths; one arm of the Y so formed joins the medial longitudinal bundle and is distributed to the ocular nuclei; the other passes to the cerebellar nuclei via the middle cerebellar peduncle.

EFFECTS FOLLOWING LABYRINTHECTOMY (IN THE DOG)

Unilateral labyrinthectomy. (1) *Ocular.* Both eyes are turned toward the side of the operation. The eye of this side also shows a downward deviation while the eye of the sound side deviates upwards (skew deviation). *Horizontal nystagmus* (p. 839) with the slow movement toward the operated side.

(2) *Lateral flexion and rotation of the occiput* to the operated side together with flexion of the thorax on the pelvis toward this side.

(3) *The extensor tone of the limb muscles* is greater on the sound side than on the operated side, the limbs of this side being flexed and adducted, whereas those of the opposite side are extended and abducted.

(4) *Spontaneous movements.* These are all toward the operated side and consist of (a) circling, i.e., turning of the body around a vertical axis, (b) rolling, i.e., rotation around a horizontal axis; in the rabbit the rolling movements are very violent, (c) side to side movements of the head (head nystagmus), (d) falling to operated side, (e) stepping gait.

Many of the foregoing features, e.g., nystagmus, rolling and circling movements, are *irritative* in nature, i.e., the result of irritation of nerve endings by the operative trauma. They therefore improve with time. The others, e.g., oscillating movements of the head, head torsion, stepping gait, falling and asymmetrical distribution of

tone, are deficiency phenomena.¹⁰ These, for the most part, also improve since they tend to be compensated by visual and other non-labyrinthine reflexes, especially in higher animals, who also learn to exercise cerebral control over the abnormal muscular activity.

Bilateral labyrinthectomy produces irritative effects similar to those described above, the direction of the movements being variable and dependent upon which ear shows the greatest degree of irritation. The labyrinthine static reflexes are, of course, abolished but in the more intelligent animals the defects of orientation are largely compensated for by visual reactions. The normal reactions to rotation (p. 839) are abolished.

AN ANALYSIS OF LABYRINTHINE FUNCTION

The *cristae* of the semicircular canals are organs of *kinetic sense* and are responsible for the compensatory movements of eyes and limbs—stato-kinetic reflexes—to be described. The macula of the utricle is an organ of *static sense*. Upon it depend the righting and stato-tonic reflexes. The cristae of the canals respond only to changes in *velocity* (acceleration or retardation) of a rectilinear motion or to changes in *direction* of a movement, i.e., any curvilinear motion (angular acceleration). Uniform movement produces no labyrinthine reaction or any sensation. For example, when one travels with closed eyes in a straight line and perfectly smoothly, i.e., in the absence of changes in velocity which would cause jolts, the motion is unperceived. A sensation is at once aroused by a change in speed, provided that it occurs with a certain degree of suddenness; and a reflex muscular movement may result. A sensation is also aroused if the line of travel curves to one or other side, upward or downward. Tait and McNally found that in the frog, the movement to be effective must occur above a certain minimum speed, a slow rotation or tilting was not followed by a compensatory reaction.

Stimulation of the sensitive hair cells of the cristae is brought about through the effect which the movement of the head exerts upon the endolymph within the canal. The canals are stimulated by a rotation of the head in their respective planes but not by rotation in other planes; thus

¹⁰ Cocaine injected into the labyrinth produces the deficiency phenomena characteristic of labyrinthectomy, but when applied to the nerve stump after removal of the labyrinth it prevents the occurrence of the irritative phenomena.

the horizontal canals are stimulated by rotation in the horizontal plane, the vertical canals by rotation in the sagittal or frontal plane.

The canals are of capillary size (0.1 to 0.2 mm. in diameter in man) and the endolymph is of relatively high viscosity (2 to 3 times that of water). The membranous labyrinth is a practically closed system and is supported on the outside by perilymph, and the unyielding walls of the osseous labyrinth. These facts would seem to preclude the possibility that any current could be set up in the endolymph by a linear movement of the head which could act as a stimulus to the hair cells. On the other hand, a rotary movement of the head might possibly set up a current since each canal, through its communication with the utricle, constitutes virtually a circular system. Nevertheless, models made upon the plan of the canals and filled with fluid and then rotated do not show any



FIG. 354. Position taken up by a frog placed on a rotating disc during rotation to the left (from Camis after Ewald).

movement of the fluid in the nature of a continuous current. It was found, however, that as a result of its inertia a slight displacement of the fluid in relation to the walls of the tube occurred during rotation. The displacement, of course, was in a direction opposite to that of the rotary movement. When the motion was abruptly stopped, the fluid as a result of its momentum exhibited a displacement in the reverse direction, i.e., in the same direction as the previous rotation. Direct observations of the endolymph in the living animal after the introduction of a few particles of lamp black into the canal also revealed displacement during and at the end of rotation. It is concluded therefore that the pressure changes resulting from such displacements of the endolymph provide the adequate stimuli for the hair cells of the cristae. (See also Ewald's Experiment, p. 845).

A differentiation of the functions of the two sets of canals (horizontal and vertical) has been made possible by the experiments of McNally and Tait.

Working with frogs, these observers succeeded in denervating all six canals without damage to other parts of the labyrinth. Denervation of the canals individually and in pairs was also performed. They found that after the function of the canal system on both sides had been completely abolished, the animal assumed a normal posture manifesting no forced movements or disturbance of equilibrium if left undisturbed. However, a quick rotary movement around a vertical, transverse or antero-posterior axis did not cause the usual compensatory reactions of the head and limbs. A rotary movement around a transverse or antero-posterior axis is caused by tilting a table upon which an animal is resting forward or backward, or sideways. McNally and Tait conclude as a result of their experiments that the horizontal canals respond only to angular acceleration in the horizontal plane, a particular canal being stimulated when its *unexpanded portion* is advancing and its ampulla bringing up the rear; the vertical canals respond to angular acceleration in their respective planes as well as to linear acceleration, as by a movement forward, backward or sideways of the surface upon which the animal is resting; a given canal is stimulated most powerfully when the *ampullary end* is advancing.

Stimulation of a horizontal canal affects the musculature of both sides of the body and thus enables the body to resist being turned to one or other side. When, for example, an animal such as the frog (see fig. 354) is rotated to the left around a vertical axis the head turns to the right; the limbs of the left side are at the same time extended while those of the right side are flexed. The animal may walk around toward the right, that is, in a direction opposed to that of the rotary movement.

The muscular response following stimulation of a vertical canal is confined to one side of the body. Each of the four vertical canals when stimulated by tilting the animal, in the appropriate plane, causes contraction of the muscles of the corresponding quarter or "corner" of the body. Thus stimulation of the left anterior vertical canal, as by tilting diagonally forward and to the left (displacement of endolymph away from ampulla), causes contraction of the muscles of the left forelimb. The left posterior canal is concerned with movements of the left hind limb; stimulation of the right vertical canals govern in a corresponding manner the limb muscles of the right side. The vertical canals thus serve to maintain the normal orientation of the head in relation to the horizontal plane.

By causing contraction of the musculature of the appropriate limbs they counteract a force tending to upset the body in a forward, backward or lateral direction, i.e., they prevent rotation of the body in a vertical plane and thus keep it upon an "even keel."

The maculae. By centrifuging a guinea pig (at a rate of 1,000 to 2,000 revolutions per minute) it is possible to detach the otolithic membranes. An animal so deprived of its otolithic organs retains its labyrinthine reactions resulting from acceleration (stato-kinetic reflexes), but has lost its stato-tonic reflexes. McNally and Tait also found that unilateral injury of the utricle caused loss of muscular tone upon that side, the limbs becoming flexed. The body is curved and the head inclined to the injured side. The limbs of the opposite side are extended and the animal makes forced circling movements toward the side of the injury. A bilateral utricular injury resulted in great impairment of the righting reflexes, the animal being unable to maintain the normal position of the body against gravity. On the other hand, functional ablation of the semicircular canals causes no disturbance of the static postural reactions.¹¹ The adequate stimulus for the *utricular maculae* is, apparently, a gravitational pull of the otolithic membrane away from the hair cells. The maximal tonic effect upon the extensor muscles is exerted when the animal is supine with head extended, i.e., when the maculae are horizontal with the otoliths hanging from the hair cells. The minimal tonic effect is exerted when the animal is prone with head flexed (p. 831), i.e., when the maculae are horizontal with the otoliths resting upon the hair cells. The functions of the *saccular maculae* are not definitely known. McNally and Tait denervated the saccular maculae of the frog but observed no disturbance of either static or dynamic postural reactions. Parker and later Maxwell destroyed the saccules in the dog fish but no disturbance of equilibrium resulted. De Kleijn and Versteegh succeeded in destroying both saccules in the rabbit, after which all the labyrinthine reflexes could be evoked. This part of the labyrinth is possibly associated with cochlear rather than with

postural function. Tait suggests that it is an organ for the registration of vibrations in the head, i.e., vibration through bone as distinct from vibration through air. The appreciation of the sound of one's own voice may possibly depend therefore upon saccular as well as upon cochlear function.

The following is a *summary* of the respective functions of the canals and utricular maculae.

(a) *Semicircular canals*, i.e., the cristae of the ampullae, are responsible for the reactions resulting from a rectilinear or rotary *movement*, e.g., the compensatory *movements* of the eyes (see below) and limbs. (b) The *utricular maculae* are responsible for the reactions resulting from *position*, e.g., labyrinthine stato-tonic reflexes, righting reflexes and for the compensatory *positions* of the eyes. Utricular impulses serve to maintain the position already induced by stimulation of the canals.

METHODS OF STIMULATING THE LABYRINTH

In order to demonstrate the stato-kinetic reactions in animals, the semicircular canals may be excited by any one of the following modes of stimulation: (1) Rotation of the body. (2) Caloric—syringing the ear with hot or cold water. (3) Galvanic. (4) Mechanical. The first three of these means of stimulation are applicable to man.

(1) Rotation

The threshold for the perception of rotation is from 1° to 2° acceleration per second.

Rotary excitation of the canals results in four groups of reflex effects: (a) nystagmus, (b) vertigo, (c) reactions of the limbs and body, (d) reactions of the autonomic nervous system.

(a) NYSTAGMUS. If a normal person is rotated rapidly (10 turns in 10 seconds) on a revolving chair with the eyes closed, an involuntary rhythmic movement of the eyes is seen when the motion is stopped and the subject opens his eyes. The oscillation of the eyes, which is called nystagmus, lasts for about 20 seconds (normal range 15 to 35 seconds). (Nystagmus may also be induced by caloric or galvanic stimulation of the canals or may result when the eyes attempt to "fix" rapidly moving objects, as in looking from a moving vehicle.) Nystagmus consists of two components, a slow movement in one direction and a rapid movement (jerk) which returns the eye to the primary position, i.e., to its normal forward-looking position. In the nystagmus of vestibular origin the slow movement is a reflex (stato-kinetic) resulting from stimulation of the semicircular canals and is an

¹¹ The otocyst of the prawn is homologous to the utricle of mammals. It is open to the exterior and at moulting time its lining is shed. The otoliths consist of grains of sand which the animal itself introduces into the otocyst. If, after moulting, the animals are placed in a dish containing fine iron filings these are inserted and various forced movements of the head and body can be induced by bringing a magnet into relation with the ear.

attempt to keep the visual fields fixed when the head is moved (p. 833). The rapid component is cerebral in origin; the cortical centers recognizing, as it were, the deviation of the eyes and their false position in relation to the head, bring them back each time to the correct position. Under anesthesia the rapid component disappears, the

of the horizontal and rotary forms; up or down in the vertical type. The rapid, not the slow (vestibular), component is used to indicate the direction of the nystagmus. Thus, a horizontal movement with the rapid component to the subject's right is spoken of as a *right* horizontal nystagmus; one with the rapid component to the subject's left is spoken of as a *left* horizontal nystagmus.

When a subject is rotated, the movement causes a displacement of the endolymph in those canals which are in, or nearly in, the plane of rotation. When, for instance, the head is bent forward 30° the external (horizontal) canals are actually horizontal (fig. 355) and for the first 10 turns or so the endolymph is displaced in a direction opposite to that in which the canal is moving. Thus,



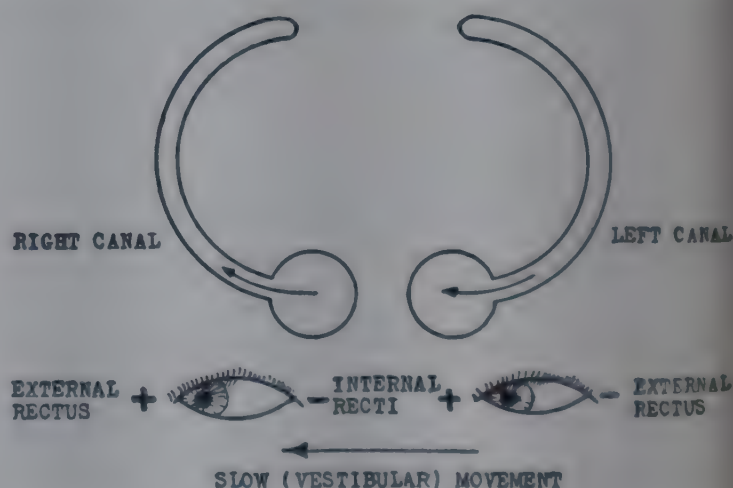
FIG. 355. Positions during rotation. Upper, horizontal canals in plane of rotation. Lower, vertical canals in plane of rotation. V, vertical canals; H, horizontal canal.

vestibular component then producing a sustained deviation in one or other direction.

Nystagmus is of three varieties, (a) *horizontal* in which the eyes move from side to side, i.e., in a horizontal plane, (b) *vertical* in which they move upwards and downwards, i.e., in the sagittal plane of the skull, and (c) *rotary* with the eye movement in the frontal plane of the skull. The rapid component may be to the right or left in the case



After this, the inertia or lag of the endolymph is overcome; fluid and canal move together. Upon stopping the rotation, the momentum of the endolymph causes it to move in relation to the wall of the canal in a direction opposite to that of its initial displacement, i.e., in the direction of the preceding rotation. Horizontal nystagmus results.



It should be mentioned that owing to the reversed position of the two external canals in relation to the direction of rotation, the endolymph is displaced toward the ampulla of one canal but away from the ampulla of the other. The direction of the slow movement of the nystagmus, it will also be noted,

is the same as that of the endolymph displacement. The rapid movement is of course in the opposite direction.

Vertical nystagmus (i.e., movement of eyes in the sagittal plane) results when the rotation is carried out with the head flexed to one or other shoulder at an angle of 90° so as to bring the vertical canals nearly into the plane of rotation; the head is thus rotated in the sagittal plane. Rotary nystagmus (movement of eyes in frontal plane) is induced by rotation with the head bent forward 120° or backward 60° , the head being then rotated in the frontal plane (fig. 355).¹² The effects of rotation upon the ampullae of the vertical canals in these different positions of the head are most complicated; the eye reactions represent the resultant of the effects in all four canals and cannot be analyzed in detail here. It is to be remembered that since the vertical canals are joined by a common stem one cannot be influenced entirely independently of the other.

In connection with the production of post-rotary nystagmus the following general rules may be summarized.

(1) The slow (vestibular) movement of the eyes after rotation has the same direction as that of the endolymph displacement, i.e., of the previous rotary movement. The rapid movement is then, of course, opposite in direction to that of the rotation. The crista of a horizontal canal, though stimulated by an endolymph movement away from it, is stimulated much more powerfully by a movement of the fluid towards it.

(2) The cristae of the vertical canals are stimulated by an endolymph displacement in either direction, but more powerfully by one *away* from the ampulla.

(3) The horizontal canals of the two sides are in the same plane. The anterior vertical canal of one side is in the same plane with the posterior vertical canal of the opposite side. The vertical canals of the same name (anterior or posterior) on the two sides or of different names on the same side are in different planes.

(4) The pressure of the endolymph in two canals in the *same* plane (e.g., horizontal canals or an anterior and a posterior vertical canal of opposite sides) is in opposite directions (toward the crista in one ear and away from it in the opposite ear).

(5) The pressure of the endolymph in any two vertical canals in *different* planes may be in the same or in opposite directions (i.e., toward or away from the cristae), depending upon the position of the head during rotation.

¹² This is of course equivalent to rotating the body around its antero-posterior axis (in the frontal plane of the skull) when the head is in its normal relation to the trunk.

(6) The horizontal canals are connected with the internal and external recti; the anterior vertical canals with the inferior and superior recti; the posterior vertical canals with the inferior and superior obliques.

(7) Stimuli of opposite sign (i.e., pressure toward the crista of one canal and away from the crista of the other) in two canals in the same plane act synergically. For example, if the endolymph moves toward the ampulla of the left horizontal canal and away from that of the right canal, the internal rectus of the left eye and the external rectus of the right eye contract while their antagonists relax—reciprocal innervation; slow movement of the eyes to the subject's right occurs (diagram p. 840).

(8) Stimuli of the same sign in a pair of vertical canals in different planes (e.g., in anterior and posterior canals of the same side or canals of the same name of opposite sides) act antagonistically—they tend to counteract one another's effects.

(9) In stimulation of the vertical canals, (a) if the pressures in each unilateral pair of vertical canals (anterior and posterior of the same side) are opposite in direction in relation to the cristae, but in the same direction in each bilateral pair of canals (the two anterior or the two posterior canals of opposite sides) the nystagmus is vertical. This occurs when the subject is rotated with head on one shoulder. (b) When the pressures in a unilateral pair are in the same direction in relation to the cristae but opposite in direction in the bilateral pairs the nystagmus is rotary. This occurs when the subject is rotated with head forward 120° or backward 60° . (See table 77.)

(b) VERTIGO. Vertigo consists of the familiar whirling sensation or giddiness, and the disturbances of equilibrium which follow spinning. When the subject is rotated with head erect, his vertigo is in the horizontal plane, i.e., in the plane of the external canals but in the direction opposite to that of the previous rotation (sensation of counter-rotation); it is therefore *in the opposite direction to that of the endolymph movement and of the slow (vestibular) movement of the post-rotary nystagmus*. The surrounding objects appear to the subject to whirl around with him, i.e., in the same direction as that of his own sensation of rotation.

If the subject is rotated with the head bowed forward at an angle of 120° (fig. 355, p. 840) to bring the vertical canals into the plane of rotation, and the head maintained in this position after rotation, the sensation is the same as if the head position had been upright during rotation, i.e., one of counter-rotation. If, however, the head is brought upright after rotation there is then a sensation of falling to one or the other side, i.e., of rotation of the body in the frontal plane; the sensation is of falling to the side away from that

TABLE 77





















POSITION OF HEAD	STIMULUS	ENDOLYMPH DISPLACEMENT IN HORIZONTAL CANALS		TYPE AND DIRECTION OF NYSTAGMUS (RAPID PHASE)	SENSATION OF VERTIGO, HEAD UPRIGHT AFTER ROTATION	PAST- POINTING	FALLING (AFTER BRINGING HEAD UPRIGHT)
		RIGAT	LEFT				
Upward or forward	Rotation to right 			Horizontal, left	Turning left	To right	
	Rotation to left 			Horizontal, right	Turning right	To left	
Backward 60°	Rotation to right 			Rotary, right	Falling right to	To left	To left
	Rotation to left 			Rotary, left	Falling left to	To right	To right
Forward 120°	Rotation to right 			Rotary, left	Falling left to	To right	To right
	Rotation to left 			Rotary, right	Falling right to	To left	To left
Inclined to right shoulder	Rotation to right 			Vertical, downward	Falling forward	Upward	Backward
	Rotation to left 			Vertical, upward	Falling backward	Down- ward	Forward
Inclined to left shoulder	Rotation to right 			Vertical, upward	Falling backward	Down- ward	Forward
	Rotation to left 			Vertical, downward	Falling forward	Upward	Backward

TABLE 77—Continued

POSITION OF HEAD	STIMULUS	ENDOLYMPH DISPLACEMENT (IN HORIZONTAL CANALS)	TYPE AND DIRECTION OF NYSTAGMUS (RAPID PHASE)	SENSATION OF VERTIGO, HEAD UPRIGHT AFTER ROTATION	PAST-POINTING	FALLING (AFTER BRINGING HEAD UPRIGHT)
Backward 60°	Caloric 112°F. to right ear or 68°F. to left.		Horizontal, right	Falling to right	To left	To left
Forward	Caloric 112°F. to left ear or 68°F. to left.		Horizontal, left	Falling to left	To right	To right
	Galvanic		Mixture of horizontal and rotary. Direction same as that of current. The responses occur only during the passage of the current.			

As an aid to memory it may be pointed out that in the erect, or forward position of the head the slow (vestibular) phase of the nystagmus and the past pointing are in the same direction as that of the rotation, i.e. in the direction of the endolymph displacement at the end of rotation. The rapid phase and the vertigo are in a direction opposite to that of the rotation, i.e. against the endolymph movement. Caloric stimulation with the head upright causes a rotary nystagmus with its direction away from the side of the syringed ear, in the case of cold douching, and toward this side in the case of hot douching. The sensation of falling is in the same direction as the nystagmus, while the past pointing and actual falling are in the opposite direction i.e., to the side of the syringed ear with cold douching and away from it with hot douching. In the above table, right and left means the patient's right and left sides.

toward which the body had been rotated. Rotation with the head bent backwards to an angle of 60° and then brought upright gives a sensation of falling to the same side as that toward which the body had been rotated (see table 77). A sensation of falling forward or backward (i.e., rotation in the sagittal plane) results from rotation with the head flexed on one shoulder and then brought upright.

Vertigo therefore differs from nystagmus which is not affected by the post-rotary position of the head. The reason for this difference is that, whereas nystagmus is reflex, the sensations of vertigo are largely the result of cerebral interpretation of endolymph movement and the position of the head at the moment is taken into account. The cerebral cortex through past experience has associated a displacement of endolymph in one direction with a movement of the head in the opposite direction; a post-rotary displacement of endolymph to the left in the horizontal canals is, therefore interpreted as a turn of the head to the right, and vice versa. Similarly, a post-rotary movement of endolymph in the vertical canals while the head is upright is interpreted as a rotation of the body in the frontal or in the sagittal plane (falling to one side or forward or backward), according to the position of the head during the rotation, for in the ordinary upright position the receptors in the vertical canals are stimulated in the same manner by a movement of the head in the respective plane.

Vertigo arises from other causes than rotation. It occurs as a result of alcoholic intoxication, sea-sickness, swinging, etc. Also, just as the labyrinth influences the movements of the ocular muscles, so, conversely, labyrinthine function may be disturbed and vertigo produced as a result of some unusual or abnormal action of the eye muscles. Vertigo and its associated phenomena are, therefore, common effects of eye strain or of viewing the landscape from a moving train; an ocular element is also an important contributory factor in the causation of sea-sickness. It should also be emphasized that with whatever condition vertigo is associated, whether cardiovascular, renal, toxic, gastrointestinal or neurological, its immediate cause is excitation of the semicircular canals or of their central connections.

(C) POST-ROTARY REACTIONS OF THE LIMBS AND BODY.

The past-pointing test of Barany. Under ordinary circumstances a normal person if he places his finger upon a certain spot has no difficulty in hitting the mark again with his eyes closed. After rotation, though able to place his finger upon a mark with his eyes open, he cannot find it again when his eyes are closed. The finger *deviates* or

past-points to one or other side, or above or below the mark, the direction of the miss-aim being dependent upon the direction of the previous rotation and upon the position of the head during rotation (see table 77). Past-pointing is not reflex in nature but is a voluntary motor act, the error in judgment is the result of the associated subjective phenomenon of vertigo, a subconscious correction being made in the opposite direction for the false sensation. The deviation of the finger and the vertigo are therefore in opposite directions, the former being toward the same side as the slow movement of the nystagmus, i.e., *in the direction of the endolymph displacement*.

Other post-rotary reactions. If the body is rotated in the plane of the horizontal canals and the movement stopped, the head (eyes closed) then turns in the direction of the rotation. If rotation



FIG. 356. So-called 'discobolus' position resulting from caloric or galvanic excitation of the labyrinth (from Camis after Wodak and Fischer).

is carried out with the head in one or other plane of the vertical canals and the head after rotation is brought upright while the eyes are closed, the body leans to one or other side, backward or forward, according to the position of the head during rotation. The subject may actually fall in the direction to which the body leans. The phenomenon is virtually a past-pointing of the entire body. The actual fall is, therefore, opposite in direction to the vertiginous sensation of falling. That is, the subject leans from the erect position in an effort to counteract the false sensation of falling in the opposite direction.

One particularly interesting reaction resulting from excitation of the semicircular canals is that which has been appropriately called the *discobolus* attitude (fig. 356). Though occurring after rotation it is evoked most readily by caloric (especially

cold) or galvanic stimulation of the canals. stimulus applied, say to the left ear, causes twisting of the thorax upon the pelvis and rotation of the head to the stimulated side. When the arms are raised they are also turned toward the side with the left limb lower than the right. After a short time the attitude is reversed, the body swings round and takes up a position in the opposite direction. The attitude may reverse its direction several times. It is due to reflex alterations in tone of the musculature on the two sides of the body.

(d) REACTIONS OF THE AUTONOMIC NERVOUS SYSTEM. Excitation of the semicircular canals in man is not uncommonly followed by nausea, vomiting and pallor. A fall in blood pressure of 10 mm. or so may occur, together with slowing of the heart by 8 or 10 beats per minute. In the rabbit, syringing the ear causes vasodilatation and a fall in blood pressure. During rotation the pupil constricts; pupillary dilatation occurs upon cessation of the rotary movement.

Camis has shown that after labyrinthectomy, the usual effect upon blood pressure of stimulating the central end of the vagus is reversed. For example, the effect of stimulating the central end of the vagus in the normal dog is frequently a rise in blood pressure accompanied by vasoconstriction of the vessels of the hind limb. After unilateral labyrinthectomy stimulation of the central end of the vagus on the operated side causes a fall in blood pressure together with a reduction of limb volume on the same side. Stimulation of the vagus in a bilaterally labyrinthectomized animal results in a fall in blood pressure and a reduction in volume of both limbs—a relationship between blood pressure and limb volume which is the reverse of the normal (p. 251). There is no satisfactory explanation of these paradoxical reactions. Camis suggests that labyrinthectomy abolishes the activity of the vasoconstrictor center. Stimulation of the central end of the vagus would then result in pure vasodilator effects, and a fall in blood pressure. The reduction in the volume of the limb may be simply a passive effect—the drainage of blood from its vessels. Bayliss found, for example, that after removal of the abdominal sympathetic (constrictors to the vessels of the abdomen, and hind limbs), a fall in blood pressure, accompanied by a reduction in limb volume resulted from stimulation of the central end of the vagus.

(2) Caloric stimulation

The effects of caloric stimulation are similar to those following rotation but possess an advantage in that one or other ear can be examined separately. The ear to be tested is syringed with hot (112°F.) or with cold

68°F.) water.¹³ When the head is bent backward through 60° the horizontal canals are brought into a vertical position. The douche causes a greater change in the temperature of the endolymph in the part of the canal lying nearer to the external meatus than in the part more deeply situated. Convection currents are set up which stimulate the crista and horizontal nystagmus and vertigo result. The change in temperature in the canal follows the irrigation of the external meatus by about 3 seconds. The direction of the convection currents, which of course are due to changes in the specific gravity of the endolymph resulting from heating or cooling, is determined by the temperature of the douche fluid. Thus a cold douche causes currents away from the ampulla, a hot douche causes ones toward the ampulla (see table 77). Caloric stimulation of the vertical canals is effected by douching with the head upright.

(3) Galvanic stimulation

In the employment of this method of stimulating the canals electrodes are placed one upon each mastoid process or, more usually, one on a mastoid process and the other on some indifferent part of the body. The current required in normal persons is from 2 to 7 milliamperes. Nerve endings in all six canals are excited by galvanic stimulation. The resulting nystagmus is a mixture of the horizontal and rotary forms, its direction being the same as that of the current. Thus, when the cathode is on the right the nystagmus is to the right and vice versa. The effects occur only during the make and break of the current. In the absence of the labyrinth the galvanic current produces its effects by stimulation of the vestibular nerve. Consequently when, as the result of disease, labyrinthine function has been destroyed, this method affords a means of determining the condition of the nerve.

(4) Direct mechanical stimulation of the canals in animals

Ewald cemented a metal cylinder over a hole made in the bony wall of the horizontal canal. A piston fitted into the cylinder could be operated by air pressure. During the descent and ascent of the pneumatic hammer the membranous canal was compressed and decompressed respectively. The endolymph during compression and decompression moved, respectively, toward and away from the ampulla. An endolymph movement toward the ampulla caused a movement of the head and eyes to the opposite side. Decompression caused a weaker movement in the reverse direction.

VESTIBULAR REACTIONS IN DISEASE

Abnormal vestibular reactions are seen in various diseased conditions involving (a) the laby-

¹³ Douches much nearer the body temperature than these will stimulate.

rinth, (b) the vestibular nerve, or (c) the vestibular centers or central pathways (e.g., Deiter's nucleus, medial longitudinal bundle, cerebellum). Normally, some slight nystagmus may occur upon looking for a time to the right or left, but if nystagmus is present when looking forward or if pronounced when the eyes are turned to one side, it is pathological. A spontaneous vertical nystagmus suggests a lesion of the brain stem; it is not seen in disease of the labyrinth itself or of the vestibular nerve. The phenomenon of past-pointing, unless induced artificially, is always pathological and suggests a cerebellar lesion. Spontaneous vertigo and falling in one or other direction may result from disease of the cerebellum, the labyrinth or the pathways of the vestibular fibers. On the other hand, a lesion in one or other of these situations may cause a failure of the usual reactions following rotary or caloric stimulation. In deaf mutes, the labyrinthine reactions, as a rule, are absent. Again, the reactions to artificial stimulation may be abnormal; for example, in a lesion of the brain stem vertical nystagmus may occur in response to a stimulus which normally causes nystagmus of the horizontal type.

The following is a summary of the abnormal labyrinthine reactions with their diagnostic significance, as given by Fisher.

I. *If stimulation of a horizontal canal of one ear, (1) causes nystagmus (normal) but not vertigo, past-pointing or falling, a lesion of the inferior cerebellar peduncle of that side is suggested, (2) causes vertigo, past-pointing and falling (all normal) but not nystagmus, a lesion between Deiter's nucleus and the medial longitudinal bundle of that side is suggested.*

II. *If stimulation of the vertical canals of one ear, (1) causes nystagmus (normal) but not vertigo, past-pointing or falling, a lesion of the middle cerebellar peduncle is suggested, (2) causes vertigo, past-pointing and falling (all normal), but not nystagmus, a lesion in posterior part of the pons near the medial longitudinal bundle is suggested.*

III. *If stimulation of all the canals of one ear, (1) causes no nystagmus, vertigo, past-pointing or falling, a lesion of the labyrinth or vestibular nerve of that side is indicated, (2) causes nystagmus (normal) but not vertigo, past-pointing or falling, a lesion of the cerebellar nuclei of that side is suggested, (3) causes vertigo past-pointing and falling (all normal), but not nystagmus, it suggests a lesion of the medial longitudinal bundle.*

IV. *If stimulation of all canals of both ears causes nystagmus (normal) but not vertigo, past-pointing or falling, it suggests a lesion in the midbrain at the point of decussation of the superior cerebellar peduncles.*

MÈNIÈRE'S SYNDROME

The features of this condition are paroxysmal attacks of vertigo, noises in the ears (tinnitus) and usually deafness of the inner ear type (p. 1045). Loss of consciousness may occur. There may be spontaneous horizontal nystagmus. The sense organs of the cochlea (organ of Corti) as well as those of the semicircular canals are affected in this

disease, which leads Crowe to believe that a common factor, namely, alterations in pressure of the endolymph or in its chemical composition is the most likely cause of the symptoms. The surgical treatment of the condition consists of severing the vestibular portion of the 8th nerve in the internal auditory meatus, leaving the cochlear division intact (McKenzie; Dandy).

CHAPTER LXVII

THE SPINAL CORD AND BRAIN STEM (MEDULLA, PONS AND MID-BRAIN)

OUTLINE OF THE INTERNAL STRUCTURE OF THE CORD

In figure 361 the spinal cord is shown in cross-section. The *gray matter*, centrally placed, is in the form of an H. It is composed of a mass of nerve cell bodies and nerve fibers (dendrons and axons), mostly unmyelinated, supported by a framework of neuroglia. The ventral and dorsal portions of each lateral half of the gray mass (i.e., each arm of the H) are commonly referred to, respectively, as the ventral (or anterior) and dorsal (or posterior) horns; but since the gray matter extends throughout the length of the cord "column" is a more suitable term than "horn." In the ventral columns are situated the large bodies (100μ in diameter) of the motor neurons whose axons leave the cord by the ventral roots. Each neuron ends in a group of skeletal muscle fibers—the neuromuscular structure constituting the so-called motor unit (p. 816). In the thoracic and upper lumbar segments, the gray mass lying between the ventral and dorsal columns shows a small lateral projection. This constitutes the lateral column or horn; it contains a group of nerve cells (the *intermedio-lateral cell column*) which give rise to sympathetic (efferent) fibers. The well-defined collection of cells occupying the inner part of the base of the posterior horn is known as *Clarke's column*; this group since it is confined almost entirely to the thoracic region of the cord is also known as the *dorsal nucleus*. To the outer side of the base of the posterior column is an area where strands of white matter and prolongations in the main mass of gray matter intermingle to form a delicate interlacement. This is known as the *reticular formation* (*formatio reticularis*) and is found chiefly in the cervical region. It is continuous with the reticular formation of the medulla and pons. At the apex of the dorsal horn is a cap of gelatinous material containing groups of small nerve cells possessing many dendrites named the *substantia gelatinosa of Rolando*. The central part of the cord lies near the center of the bar or nucleus connecting the gray matter of the two lateral halves. The portions of gray matter lying in front and behind the canal are named, respectively the *anterior* and *posterior gray commissures*.

The *white matter* which completely surrounds the gray matter is composed of bundles of myelinated fibers. A deep cleft on the ventral aspect of the cord (the *anterior median fissure*) and a septum upon the dorsal aspect (*posterior median septum*) together, divide the white matter into two lateral halves. Each half is further marked out, by the fibers of the ventral and dorsal nerve roots, into three white columns or funiculi, ventral (anterior), lateral and dorsal (posterior). The *ventral funiculus* lies between the anterior median fissure on the one hand, and the ventral gray column (anterior horn) and the fibers of the ventral roots on the other. Bounded in front and medially by the last two structures, and postero-medially by the dorsal gray column and the fibers of the dorsal roots lies the *lateral funiculus*. The *dorsal funiculus* is situated between the dorsal gray column (posterior horn) and the dorsal root fibers which form its antero-lateral boundary, and the posterior median septum.

THE SPINAL NERVE ROOTS

The *anterior roots* of the spinal nerves are composed entirely of efferent fibers (p. 810).¹ These are (a) the axons of the cells of the anterior horns and (b) in the thoracic and upper lumbar regions, the preganglionic fibers of the sympathetic system already mentioned as arising from the cells of the lateral gray column. The *posterior roots* are constituted of afferent fibers from the skin, muscles and

¹ Although doubt has been expressed from time to time concerning the purely efferent nature of the fibers composing the anterior roots, no substantial evidence has been ever brought forward to show that this is not so. It is true that stimulation of the central end of an anterior root sometimes gives rise to pain, but this is due to the presence of recurrent fibers from the posterior roots and in no way invalidates the Bell-Magendie law. Neurons have been found in the anterior roots resembling those of the posterior root ganglia, but there is no evidence that they are sensory in function. Some authors have been led to believe that the anterior roots transmit sensory impulses because pain is not always relieved by section of the posterior roots. There are three possible reasons for the failure of this operation. In the first place, the pain may arise within the central nervous system itself, a filament of a posterior root may have escaped division, or innervation from adjacent spinal segments may overlap to an unusual extent; pain would then continue to be registered from the area innervated by the severed roots.

viscera. Their cell bodies lie in the spinal ganglia. There is no important evidence that they contain efferent fibers. (See Bell-Magendie law, p. 808 and also p. 236.) Two divisions of the posterior root, a medial and a lateral, are distinguished. The lateral division is largely composed of small unmyelinated fibers; these, after entering the cord form the small triangular area at the tip of the posterior horn known as Lissauer's tract (p. 849). The fibers of the medial division, which are for the most part heavily myelinated, enter the posterior columns of the cord (see fig. 361).

THE SEGMENTAL DISTRIBUTION OF THE SPINAL NERVES

In the young mammalian embryo and in certain adult lower forms, e.g., fishes, the body is demarcated into a regular series of transverse segments or *metameres*. The muscles (*myotomes*), skin (*dermatomes*) and viscera of each of these primitive blocks eventually receive innervation from the nerve roots of a corresponding spinal segment. The anterior root of each spinal nerve supplies motor fibers to the respective myotome, and autonomic fibers to the viscera and skin; the posterior root supplies sensory fibers to the corresponding dermatome as well as to the muscles and viscera. As a result of the outgrowth of the embryonic limbs the orderly arrangement of the metameres from before backwards becomes altered. In the adult mammal, the primitive metameric disposition is observed only in the trunk. The fibers of the spinal nerves supplying the limbs have joined to form the brachial and lumbo-sacral plexuses and, after intermingling freely, issue again as the peripheral nerves. The latter, in consequence, are composed of fibers derived from two or more spinal segments, and fibers from a given segment pass into several peripheral nerves. The muscles supplied by a given spinal segment do not necessarily lie in close proximity to one another (the coracobrachialis, for example, is innervated by the same segments as those which supply the muscles of the thumb) and a single muscle may derive its nerve supply from more than one spinal segment (see page 865). As development proceeds and the limbs grow out from the trunk, the dermatomes become arranged in a series of narrow areas lying for the most part in the long axis of the limb (fig. 357). The skin and muscles of the limbs also tend to move away from the visceral structures with which they were originally associated and, in the adult, innervated

originally associated and, in the adult, structures innervated by a common spinal segment may widely separated. Thus, the diaphragm is innervated (through the phrenic) from the 3, 4 and 5 cervical segments which also supply skin and muscle in the region of the neck and shoulder. The heart receives sensory and autonomic fibers from the upper thoracic segments; these segments also supply sensory fibers to the skin over the

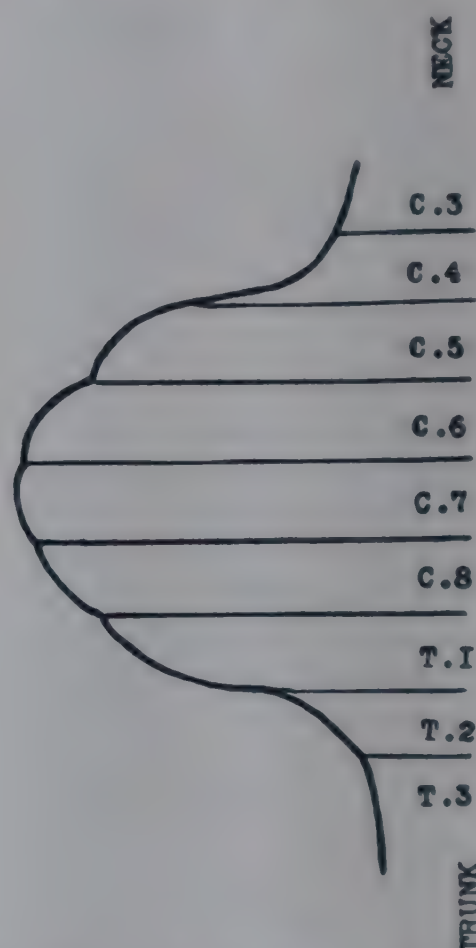


FIG. 357. Showing the drawing out of the metameres of the embryo with the development of the limb-bud (redrawn and modified from Gray, *Anatomy of the Human Body*).

aspect of the arm and hand and upper part of the thorax. The distribution of the dermatomes and cutaneous nerves in the human subject are shown in figures 358 and 359.

Several methods have been employed by different investigators in mapping out the dermatomes in animals and in the human subject. The *anatomical* method is laborious and consists in tracing the fibers of a spinal root to their termination in the skin. A *physiological* method ("isolation" or "sensory remainder" method) was employed by Sherrington in cats and monkeys. The area of skin supplied by a given segment was demarcated by dividing the sensory roots above and below. The sensitive area of skin bounded above and below by an anesthetic zone indicated the distribution of the undivided roots. Owing

overlap of fibers from adjacent segments, it is not possible to produce an anesthetic area by the division of the sensory roots of a single segment (fig. 360). Head mapped out the segmental distribution of the cutaneous nerves in the human subject from studies of cases of herpes zoster, a condition due to a lesion of the ganglion cells of the

—from higher centers to spinal neurons. (b) *short tracts* (intersegmental or association tracts, ground bundles) which begin and end within the cord and connect different spinal segments. The fiber tracts making up the substance of the respective funiculi are listed in table 78 and shown diagrammatically in figure 361.

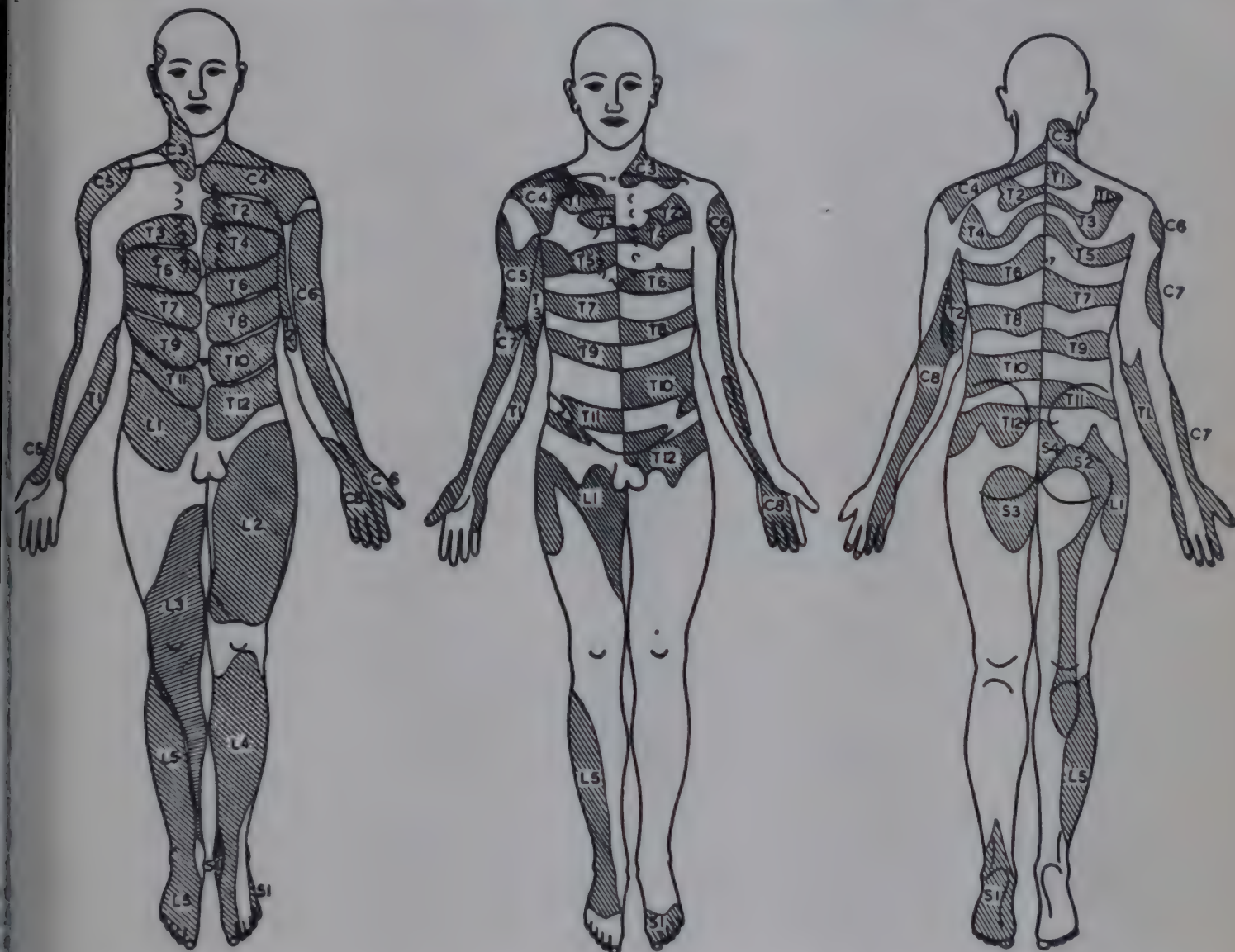


FIG. 358. The two figures to the right represent Head's cutaneous areas, as displayed in his original papers. Small areas of C5 and C6, coinciding with T1 and T3 on the back, have been omitted. The left-hand figure has been constructed from Foerster's data (49) and represents his "dermatomes". (after Lewis)

posterior roots. Within more recent years Foerster, using Sherrington's method has mapped out the dermatomes in man. He also stimulated the posterior roots at operation and used the resulting vascular reaction (vasodilatation) as the means of demarcating the dermatomes.

THE TRACTS OF THE CORD

The fiber tracts of the cord are divisible into two main groups: (a) *long tracts* (projection tracts) which connect the cord with other parts of the central nervous system. Some of these (ascending tracts) carry impulses to higher centers; other tracts (descending) conduct in the reverse direction

ASCENDING TRACTS OF THE CORD

(1) **THE DORSILATERAL FASCICULUS (TRACT OF LISSAUER).** This is seen in cross section as a small area lying between the tip of the posterior horn and the periphery of the cord (fig. 361). It is composed of fibers derived from the lateral division of the posterior nerve roots. These fibers upon entering the cord form synapses immediately, or after a very short upward course, with cells occupying the tip of the posterior horn, i.e., in the substantia gelatinosa of Rolando (p. 847). The fibers of this tract are mostly of small diameter and unmyelinated, and are believed to constitute the primary neurons in the pathway for pain and

crude thermal sensations. The axons of the secondary neurons go to form the lateral spinothalamic tract, to be immediately described

in the posterior funiculus for a variable number of segments before entering the gray matter crossing to the ventral spinothalamic tract

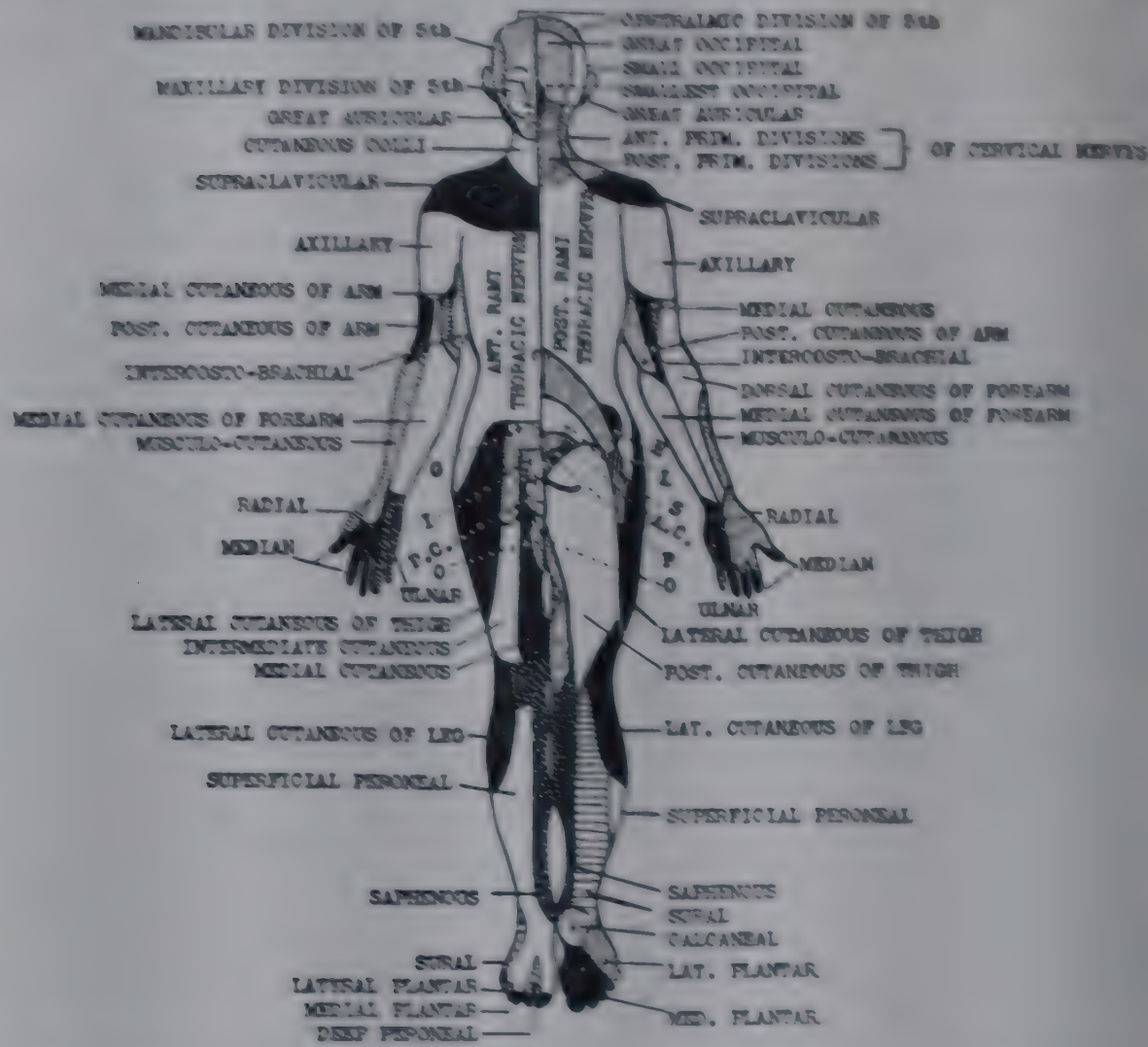


FIG. 359. Showing distribution of cutaneous nerves; anterior aspect of body on left, posterior on right. I, iliohypogastric and genitofemoral nerves; L, ilio-inguinal nerve; P-C, on left side, P, on right side, posterior cutaneous nerve of thigh; O, obturator nerve; H, iliohypogastric nerve; L, posterior branches of 1st, 2nd lumbar nerves; S, posterior branches of 1st, 2nd and 3rd sacral nerves.

(2) THE LATERAL (POSTERIOR) AND VENTRAL (ANTERIOR) SPINOTHALAMIC TRACTS. The fibers of the lateral tract arise, as mentioned above, from cells in the substantia gelatinosa of Rolando; those of the ventral tract arise from cells in the adjacent gray substance of the posterior horn. The fibers constituting these tracts, after crossing the mid-line in the anterior gray commissure, ascend respectively in the lateral and ventral white columns of the cord. The ventral spinothalamic tract is a crossed pathway for the mediation of touch, light pressure and localization (p. 853). The lateral spinothalamic tract transmits impulses aroused by all forms of thermal and painful stimuli applied to the opposite side of the body. The primary neurons in the pathway for tactile sensations after entering the cord ascend

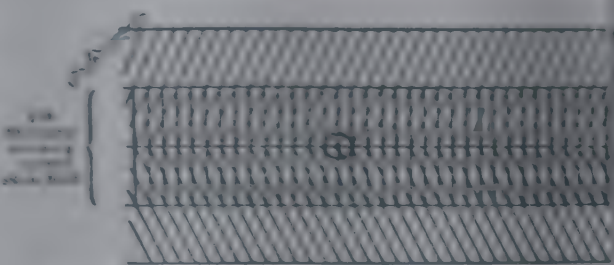


FIG. 360. Diagram showing the overlap of skin area innervated through the fourth thoracic nerve root by those supplied by the third thoracic nerve root. The small circle indicates the position of the nerve root (after Sherrington).

opposite side. As mentioned above, the neurons of the pathway for thermal and painful sensations enter the gray matter almost immediately and cross to the opposite side. The tracts come together in the medulla and ascend on the outer side of the medial lemniscus

teroventral nucleus of the thalamus (see 879).

THE SPINOTECTAL TRACT is placed in the column ventral to the lateral spinothalamic. Its fibers arise from cells in the posterior of the opposite side and terminate in the inferior colliculus. It subserves spinovisual reflexes.

SPINOCEREBELLAR TRACTS. (a) The *dorsal cerebellar tract* (direct cerebellar or tract of Goll) is situated in the posterior part of the funiculus to the outer side of the lateral spinothalamic tract. It is composed of the axons of the cells of Clarke's column (p. 847) of the opposite side. The direct cerebellar tract reaches the cerebellum via the inferior cerebellar peduncle; its fibers end mainly in the cortex of the anterior and posterior lobes of the cerebellum (p. 923). (b) The *ventral spinocerebellar tract* (indirect cerebellar or tract of Burdach) arises from the cells of Clarke's column, of the same, but also of the opposite side of the cord. It ascends in front of the dorsal cerebellar tract and is continued upwards through the brain stem as far as the mid-brain where it arches backwards and downwards (arcuate fibers) to reach the cerebellum via its superior peduncle. Its constituent fibers end in the cortex of the anterior and posterior cerebellar lobes. Spinocerebellar tracts carry impulses arising from proprioceptors of the muscles, tendons and joints. The information thus conveyed to the cerebellum is essential for the latter's function in regulating the tone of the skeletal muscles and coordinating their movements (p. 928).

THE FASCICULI GRACILIS (TRACT OF GOLL) AND THE FASCICULUS CUNEATUS (TRACT OF BURDACH) occupy the posterior funiculus of the cord, the former being medial to the latter. These tracts are composed of the heavily myelinated fibers of the posterior division of the homolateral posterior nerve roots. Which, after their entrance into the cord, divide into long ascending and short descending tracts. The latter after a short course enter the anterior horn (see fasciculus interfasicularis, p. 879). The former, as they proceed upwards, are displaced medially, with the result that those arising at lower levels (e.g., sacral region) lie closer to the midline than those entering at higher levels (e.g., cervical region). Consequently, the posterior division of the cord in the mid-dorsal region upwards the more medially placed tract (fasciculus gracilis) is composed of fibers derived from the lower thoracic, lumbar and sacral nerve roots, whereas the fasciculus cuneatus is constituted of fibers derived from

the upper thoracic and cervical nerve roots. Of the constituent fibers of the two tracts, some, after ascending for a variable number of spinal segments end in the gray matter of the cord and cross to the opposite side and ascend as the anterior spinothalamic tract. The remaining fibers of the fasciculi gracilis and cuneatus proceed uncrossed to end, respectively, in the nucleus gracilis and nucleus cuneatus situated in the lower part of the medulla. From these nuclei the axons of secondary neurons emerge and, passing medially as the *internal arcuate fibers*, decussate with those of the opposite side (sensory decussation). They ascend through the brain stem as the *medial lemniscus* (p. 854) to terminate in the lateral nucleus of the thalamus. Other fibers (*external arcuate*) from the nuclei gracilis and cuneatus relay to the cerebellum (p. 924) non-sensory impulses brought to them by the corresponding spinal fasciculi.

Summary of the principal pathways ascending through the cord

A. SENSORY. (1) The fibers mediating thermal and painful sensations enter the cord in the lateral divisions of the posterior nerve roots. According to Ranson they are unmyelinated. Within the cord they constitute Lissauer's tract. Immediately, or after a very short upward course, they enter the posterior gray column and connect with nerve cells therein. The axons of these secondary neurons cross to the opposite side in the anterior gray and the anterior white commissures and ascend as the lateral spinothalamic tract. This tract occupies a position in the brain stem lateral to the medial lemniscus and ends in the lateral nucleus of the thalamus (cf. figs. 361 and 362).

(2) The fibers conveying all other sensory impulses, e.g., from the muscles and joints (sense of movement and position), impulses for touch, pressure, tactile localization and spatial discrimination (compass test), enter the cord in the medial division of the posterior roots and ascend in the fasciculus gracilis and fasciculus cuneatus. (a) Those mediating the sense of movement and position of the limbs and spatial discrimination do not cross in the cord but pass directly to the nucleus gracilis and nucleus cuneatus where they connect with secondary neurons. The axons of the latter decussate with those of the opposite side and ascend to the thalamus as the medial lemniscus (or fillet). Tertiary neurons convey the impulses to the cerebral cortex. (b) Fibers conveying impulses

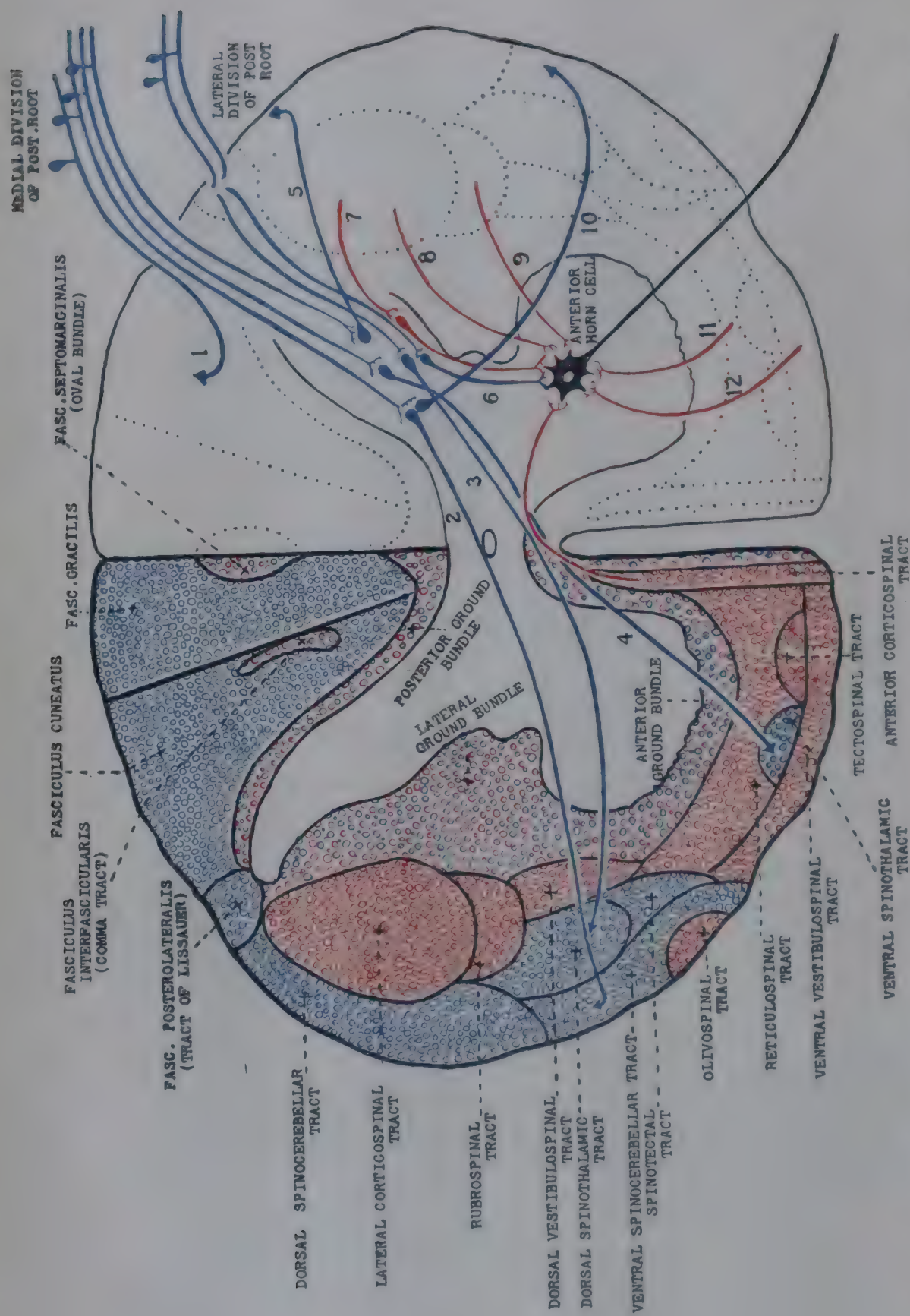


FIG. 361. Diagram to show tracts of the cord. Ascending fibers shown in blue, descending in red, spinal motoneuron in black. 1, represents fibers ascending in posterior columns (mediating sensations of touch, spatial discrimination, and of position and movement); 2 and 10, represent fibers entering the contralateral and homolateral ventral spinothalamic tracts, respectively; 3, represents fibers entering dorsal spinothalamic tract of the opposite side (mediating pain and thermal sensations); 4, represents fibers entering ventral spinothalamic tract of the opposite side (mediating touch and tactile localization); 5, fiber entering dorsal spinothalamic tract; 6, internuncial neuron connecting a posterior root fiber with anterior horn cell (reflex arc); 7 and 8, crossed corticospinal fibers connecting, respectively, through an internuncial neuron and directly, with anterior horn cell; fiber of an

for *light touch*, *light pressure* and *localization* ascend for variable distances in the dorsal fasciculi but the majority eventually connect with cells in the dorsal gray column; the axons of these cells cross

even pass uncrossed to the nuclei gracilis and cuneatus. The result is that these sensations have virtually two pathways in the cord. Therefore, in a lesion involving the dorsal fasciculi, touch,

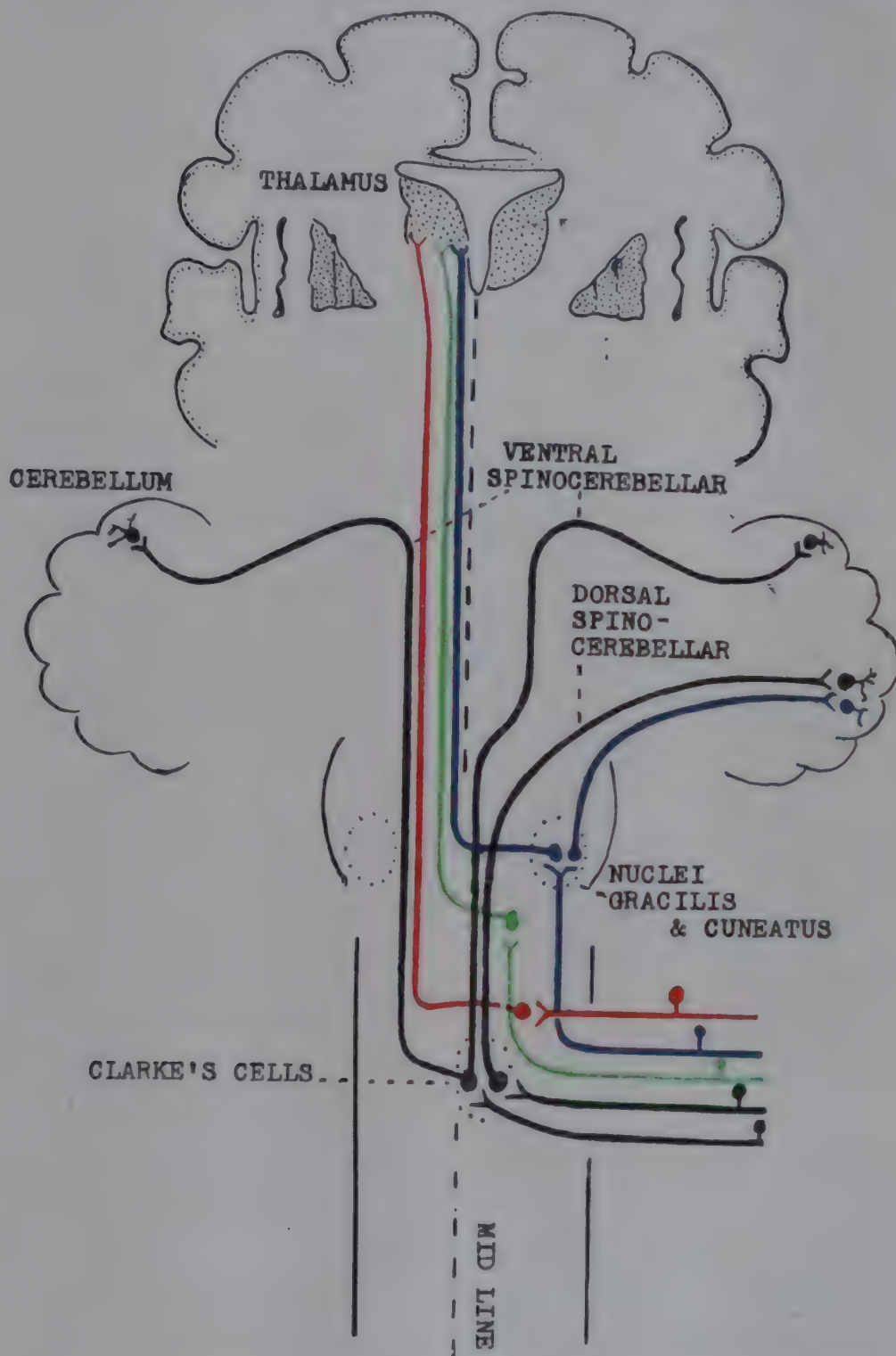


FIG. 362. Diagram showing the course of afferent impulses after their entrance into the cord. *Red*, pathway for pain and thermal sensations (ascend in dorsal spinothalamic tract of opposite side). *Blue*, pathway for touch, sense of position and movement, and spatial discrimination (ascend in posterior columns); external arcuate fibers from posterior column nuclei to cerebellum also shown. *Green*, pathway for touch, and tactile localization (after travelling for variable distances in posterior columns, fibers cross to ventral spinothalamic tract of opposite side). *Black*, ventral and dorsal spinocerebellar tracts, some fibers of latter (not shown) also cross to opposite side.

in the anterior gray commissure and ascend in the ventral (anterior) spinothalamic tract. It appears from clinical observation that of the fibers mediating these sensations from a given region of the body some cross after a short upward course, others after a much longer course, and some may

pressure and tactile localization are little affected since they are still capable of being conveyed by fibers which have already crossed (i.e., below the lesion) to the ventral spinothalamic tract (see also hemisection of the cord). Impulses subserving light touch and tactile localization, but not

the cruder sensation of skin pressure, are relayed from the thalamus to the cerebral cortex.

B. NON-SENSORY. Non-sensory impulses from the muscles, tendons and joints are conveyed into the cord by fibers composing the medial divisions of the posterior roots. These fibers connect immediately with the cells of Clarke's column and are continued upwards in the dorsal (direct) and ventral (indirect) cerebellar tracts of the same side, mainly, but also of the opposite side. Some of these non-sensory impulses are conveyed by fibers of the posterior fasciculi to the nuclei gracilis and cuneatus from where they are relayed by secondary neurons (external arcuate fibers) via the inferior peduncles to the cerebellum. (See fig. 362.)

THE REGROUPING OF AFFERENT IMPULSES IN THE CORD. It will be noted that in the cord the fibers mediating the several types of sensation are grouped without regard to the three peripheral systems, protopathic, epicritic and deep sensibility (p. 803). A regrouping occurs in which fibers conveying impulses for spatial discrimination belonging to the epicritic system ascend with those for muscle sense (deep sensibility) in the dorsal fasciculi. Those fibers mediating touch, light pressure and localization ultimately ascend together in the ventral spinothalamic tract while temperature and pain are segregated in the lateral spinothalamic tract. In the thalamus the impulses undergo a second resorting; the paths for crude sensations, e.g., of pain and of the extremes of temperature do not ascend beyond this level (p. 880). The other more discriminative qualities of sensation are continued upwards to the cerebral cortex.

SENSORY PATHS IN THE BRAIN STEM (MEDULLA, PONS AND MID-BRAIN)

The *medial lemniscus* (or fillet). This is constituted of fibers arising in the nuclei gracilis and cuneatus, that is, of the axons of secondary neurons in the pathway mediating spatial discrimination and muscle sense. The fibers leave the ventral aspects of these nuclei and arch forward and medially (as *internal arcuate fibers*) to the mid-line where they cross with corresponding fibers of the opposite side (*sensory decussation*). They then turn upwards as a compact bundle known as the medial lemniscus or fillet. This ascends through the medulla and pons dorsal to the pyramidal tracts, and through the tegmentum of the mid-brain.

The *spinal lemniscus* (or fillet) is formed by the fusion of the anterior and lateral spinothalamic

tracts and is therefore a crossed path for impulse aroused by light touch, pressure, pain, heat and cold.

The *trigeminal lemniscus* (or fillet) conveys impulses from the area of distribution of the trigeminal nerve of the opposite side (p. 857).

The fibers of the medial, spinal and trigeminal lemnisci terminate in the nucleus of the thalamus, from where tertiary neurons pass to the cerebral cortex (p. 893).

The *lateral lemniscus* constitutes the pathway for auditory impulses from the cochlear nucleus and superior olive to the inferior colliculus and medial geniculate body (p. 1024).

The sensory pathways are constituted of three neurons. The path for spatial discrimination and muscle sense, for example, consists of a primary neuron whose cell body lies in the posterior root ganglion, a secondary neuron originating in the posterior column nucleus (gracilis or cuneatus) and a tertiary neuron arising in the lateral nucleus of the thalamus. The cells of the Gasserian ganglia are the primary neurons of the trigeminal pathway; secondary neurons lie in the sensory nucleus and in the spinal nucleus of the nerve (p. 858). The spinal lemniscus is composed of the axons of secondary neurons whose cell bodies lie in the posterior gray columns of the cord; the primary neurons arise in the posterior root ganglia.

In the upper part of the medulla the medial lemniscus is joined on its outer side by the spinal lemniscus. In the pons the fibers of the contralateral sensory nucleus of the trigeminal join the medial fillet, and fibers from the opposite spinal nucleus of the trigeminal join the spinal lemniscus. In the upper part of the pons and in the mid-brain these several sensory pathways become fused together into a compact bundle. A lesion in the lower part of the brain stem may involve one of the sensory pathways exclusively of the others. Thus an injury localized to the outer part of the lower pons or of the medulla may by injuring the spinal lemniscus cause loss of sensation to pain, heat and cold over the *opposite half* of the body, leaving muscle sense and tactile discrimination intact. Sensory loss of this nature accompanied by cerebellar symptoms occurs as a result of the occlusion (as by thrombosis or embolism) of the posterior inferior cerebellar artery. Usually also as a result of the involvement of the spinal tract of the trigeminal nerve (p. 858) the face on the *same side* as the occluded vessel shows the dissociated sensory loss. A lesion more centrally placed may, by implicating the medial fillet alone, cause

the converse type of dissociated sensory defect, namely, loss of the sense of position of the limbs and of spatial discrimination with retention of sensibility to pain, heat and cold. In lesions at higher levels in the brain stem all forms

Sheehan a tract of uncrossed pyramidal fibers in the lateral column of the cord. Through these two tracts (anterior and lateral) of uncrossed fibers the skeletal muscles of each side of the body receive impulses from both motor areas of the cortex.

TABLE 78

FUNICULUS	ASCENDING TRACTS	DESCENDING TRACTS	INTERSEGMENTAL TRACTS (GROUND BUNDLES)
Ventral (anterior)	Ventral (anterior) spinothalamic	Ventral (anterior) corticospinal (direct pyramidal) Vestibulospinal Ventral (anterior) tectospinal Reticulospinal	Ventral (anterior) intersegmental fasciculus
Lateral	Lateral spinothalamic Dorsal (posterior) spinocerebellar (Flechsig) Ventral (anterior) spinocerebellar Spinotectal Dorsilateral (posterolateral) fasciculus (Lissauer)	Lateral corticospinal (crossed) pyramidal) Rubrospinal Olivospinal (Helweg) Dorsal tectospinal	Lateral intersegmental fasciculus
Dorsal (posterior)	Fasciculus gracilis Fasciculus cuneatus		Septomarginal fasciculus Dorsal (posterior) intersegmental fasciculus

sensation are likely to be involved more or less equally.

DESCENDING TRACTS OF THE CORD

(1) THE CORTICOSPINAL OR PYRAMIDAL TRACTS. The origin of the corticospinal tracts and their course through the cerebrum and brain stem are described on page 862. The tract of each side divides into two bundles at the lower border of the medulla. The larger of these crosses with the corresponding bundle of the opposite side and descends in the posterior part of the lateral funiculus of the cord as the *lateral corticospinal tract* (crossed pyramidal tract). The remaining fibers, uncrossed, descend in the anterior funiculus as the *anterior corticospinal tract* (direct pyramidal tract). The direct pyramidal tract is well marked in the cervical region but its fibers dwindle gradually in number, in successive segments. They may be traced, however, as far as the sacral region; a proportion of the fibers of this tract also cross eventually to the opposite side of the cord, passing at different levels through the anterior commissure. (Cf. figs. 361 and 363.) Besides the well-recognized anterior (direct) corticospinal tract there is, shown by Schafer and lately by Fulton and

The corticospinal fibers (crossed and uncrossed) connect with the large motor cells of the ventral gray columns (anterior horn cells). The connections are of two types, (a) direct synapses with the motor neurons, (b) indirect connections with these cells through an internuncial neuron whose cell body is also in communication with a posterior root fiber on each side (fig. 363).

(2) THE VESTIBULOSPINAL TRACTS. These are two in number; a ventral and a lateral. The *ventral vestibulospinal tract* descends in the forepart of the anterior funiculus and lateral to the anterior portion of the direct pyramidal tract. Its fibers arise from the lateral vestibular nucleus (Deiter's) chiefly of the same side, and may be traced as far as the sacral region. The fibers terminate by forming synapses with the motor neurons either directly or through an internuncial neuron. The *lateral vestibulospinal tract* is smaller. Its fibers—the axons of cells in Deiter's nucleus—descend in the lateral column of the same side. The vestibulospinal tracts form a section of the pathway from the labyrinth and the cerebellum to the skeletal muscles.

(3) THE TECTOSPINAL TRACT is composed of fibers which arise in the superior colliculus of the

opposite side and descend through the reticular formation of the pons and medulla. Upon entering the cord the tract separates into a ventral and a dorsal bundle which descend in the corresponding spinal funiculi. The fibers of this tract synapse with the motor neurons either directly or through internuncial neurons. The superior colliculus receives nerve impulses from the retina and through its connections with the spinal motor

Here the rubrospinal fibers connect either directly or through internuncial neurons with the motor neurons, to which they relay impulses from the cerebellum and striate body.

(5) THE OLIVOSPINAL (BULBOSPINAL) TRACT OF HELWEG. Its fibers arise from cells in the neighborhood of the olivary nucleus and descend in the ventral part of the lateral funiculus. They descend no farther than the cervical region. The

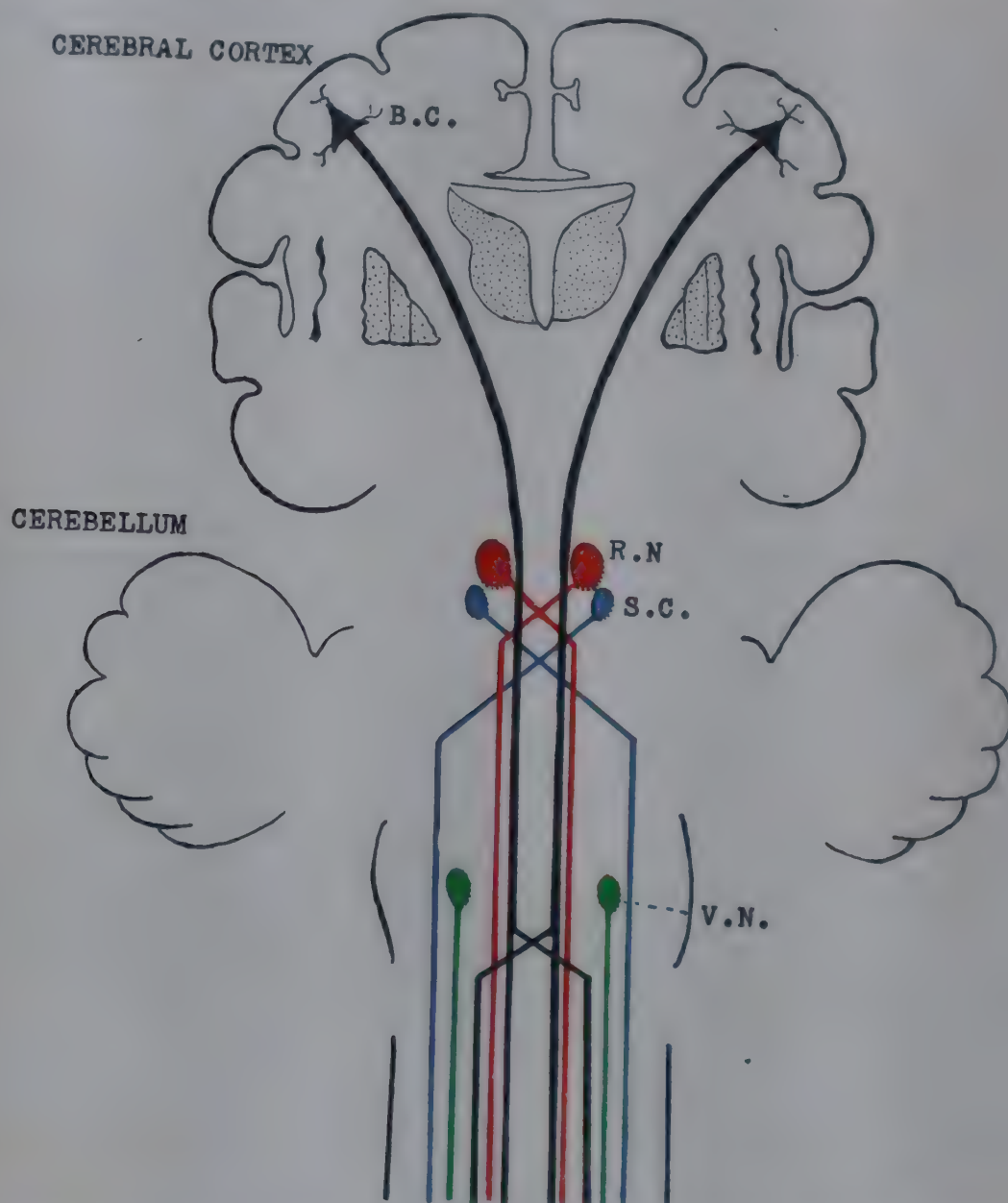


FIG. 363. Diagram showing pyramidal tracts (black), rubrospinal tracts (red), tectospinal tracts (blue) and vestibulospinal tracts (green). B.C., Betz cell of motor cortex; R.N., red nucleus; S.C., superior colliculus; V.N., vestibular nucleus.

neurons visual impulses are correlated with body movements (visuospinal reflexes).

(4) The RUBROSPINAL TRACT arises from the large cells (nucleus magnocellularis) in the posterior part of the red nucleus (p 874). The fibers immediately upon leaving the red nucleus cross to the opposite side (*Forel's decussation*) and descend through the reticular formation of the pons and medulla to enter the lateral funiculus of the cord ventral to the lateral corticospinal tract.

The fibers synapse with the motor neurons. The functions of this tract are unknown. It and the thalamo-olivary tract constitute a possible pathway whereby impulses from the thalamus may reach the spinal centers.

(6) The RETICULOSPINAL TRACTS arise from cells scattered through the reticular formation of the upper part of the pons. They are two in number, one (uncrossed) descends in the anterior funiculus and the other (crossed) in the lateral funiculus. The

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connect with the motor neurons in the anterior horns and probably with cells in the lateral horn. These tracts transmit impulses from the striate body and cerebellum.

INTERSEGMENTAL TRACTS OF THE CORD AND THE MEDIAL LONGITUDINAL FASCICULUS

There is in each funiculus of the cord lying close to the gray matter an intersegmental fasciculus or ground bundle. These, as already mentioned, serve to link up spinal segments of different levels. Their fibers arise from cells in the gray matter and after an ascending or descending course of variable length end around cells of the same or the opposite side at a higher or a lower level. The proportion of the fibers constituting the intersegmental fasciculus of the lateral column of the cord (*lateral intersegmental fasciculus* or *lateral ground bundle*) are continued upwards into the medial longitudinal fasciculus of the brain stem. The ground bundle of the anterior funiculus (*anterior intersegmental fasciculus* or *anterior ground bundle*) is composed of fibers which connect the anterior horn cells of one side with those of the opposite side both at the same and at different levels. Some of the fibers also pass upwards into the medial longitudinal fasciculus.

The posterior funiculus contains (a) the septo-marginal fasciculus and (b) the posterior intersegmental fasciculus (or posterior ground bundle).

The *septo-marginal fasciculus* is composed of intersegmental fibers which arise from cells of the posterior horn and synapse with corresponding cells at lower levels. The descending fibers of the medial divisions of the posterior nerve roots (p. 847) also enter into the constitution of this tract. The fibers of the septo-marginal fasciculus occupy different positions at different spinal levels. In the cervical and upper thoracic regions the fibers appear on section as a crescentic area at about the center of the posterior funiculus. Here they are spoken of as the *common tract* or *tractus interfascicularis*. In the lower thoracic region they form a narrow zone bounding the posterior part of the cord and known as the *dorsal peripheral band*. In the lumbar region they appear on section as a semi-oval mass—the *oval area of Flechsig*—abutting against the posterior median septum.

The *posterior intersegmental fasciculus* is seen in cross section as a small area lying behind the posterior gray commissure. Its fibers connect the posterior horn cells of different segments (see fig. 361).

THE MEDIAL LONGITUDINAL FASCICULUS

The medial (posterior) longitudinal fasciculus (bundle) is a compact tract composed of short

ascending and descending fibers which connect the nuclei of the cranial nerves with each other (fig. 353). It is homologous with the anterior intersegmental fasciculus of the spinal cord. The tract lies near the mid-line and extends from the upper segments of the cord to the floor of the 3rd ventricle. In the medulla it lies immediately subjacent to the floor of the 4th ventricle; in the pons it courses through the *formatio reticularis*, and in the mid-brain, lies in the floor of the Sylvian (cerebral) aqueduct. It is continuous below with the ground bundles of the anterior and lateral funiculi of the spinal cord. The fasciculus receives many fibers from the vestibular nuclei (p. 836) of the same and of the opposite side, from the lateral lemniscus (auditory path, p. 1024) and from the superior colliculus, through which it is in communication with the optic pathway (p. 1009). It sends fibers to the nuclei of the oculomotor, trochlear, abducens, facial, accessory and hypoglossal nerves. Its essential function is the coordination reflex movements of the ocular and neck muscles in response to labyrinthine, auditory and visual stimuli.

THE CENTRAL CONNECTIONS OF THE TRIGEMINAL, FACIAL, GLOSSOPHARYNGEAL, VAGUS, ACCESSORY AND HYPOGLOSSAL NERVES

The trigeminal pathway

The trigeminal nerve appears near the upper border of the ventral surface of the pons and consists of three roots (a) a large *sensory*, (b) a small *motor*, and (c) a *mesencephalic* (fig. 364).

The fibers of the *sensory root* convey impulses from the anterior part of the scalp, from the skin of the forehead and face, with the exception of an area over the angle of the mandible, and from the upper half or so of the pinna. It also supplies the mucous membrane of the mouth (anterior two-thirds of tongue) and nose; and the cornea and conjunctivae. This root arises from the cells of the Gasserian (semilunar) ganglion. The processes of these cells divide into peripheral and central branches. The former enter into the composition of the peripheral divisions (ophthalmic, maxillary and mandibular) of the nerve; the central branches (which constitute the sensory root) enter the pons in close association with the fibers of the motor root and divide into an ascending and a descending group. (a) The *ascending fibers* convey impulses of light touch, tactile discrimination and localization, and of the sense of position and passive movement. They end in a

nucleus (*upper sensory nucleus of the trigeminal*) situated in the pons, deep and lateral to the motor nucleus. (b) The *descending fibers* constitute the *bulbospinal tract of the trigeminal*. They subserve sensations of pain and temperature over the entire trigeminal area. They descend through the pons and medulla and may be traced as far as the 2nd cervical segment. This tract dwindles gradually in its descent, its fibers terminating around cells in a mass of gray matter in relation to it. This collection of gray matter is known as the *spinal nucleus of the trigeminal*. The fibers of the mandibular, maxillary and ophthalmic divisions of the trigeminal end in the nucleus in this order

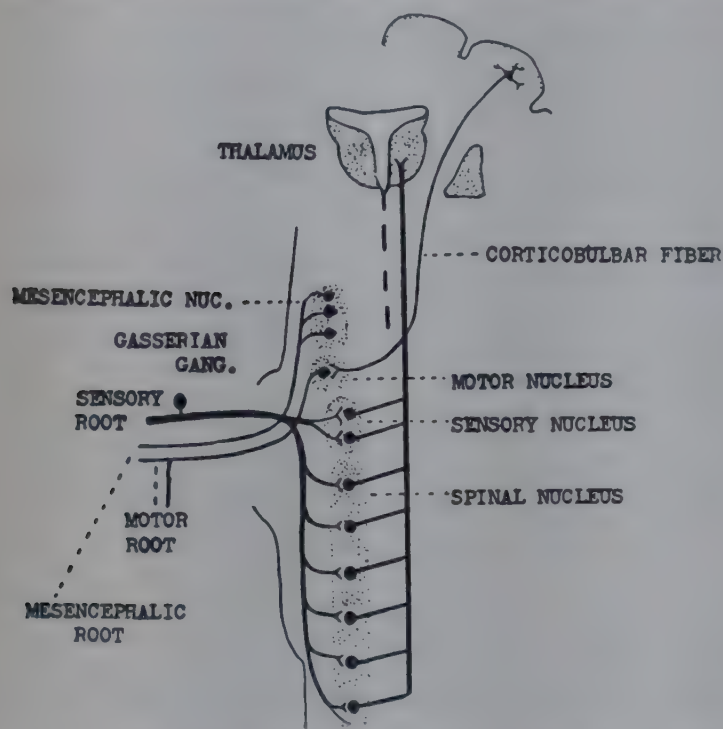


FIG. 364. Diagram of the central connections of the trigeminal nerve.

from above downwards, that is, in an order the inverse of that in which they are distributed to the skin of the face. From the spinal nucleus the axons of secondary neurons emerge which cross the mid-line; ascending, they join fibers arising from the upper sensory nucleus to form the trigeminal lemniscus (or fillet). The trigeminal lemniscus lies in close association with the spinothalamic tracts and medial lemniscus (p. 854); its fibers terminate in the posteroventral nucleus of the thalamus.

The upper sensory nucleus of the trigeminal corresponds to the nuclei of the posterior columns of the cord (nuclei gracilis and cuneatus) and like the latter sends fibers to the cerebellum through the inferior cerebellar peduncle. The spinal tract of the trigeminal may be looked upon as corresponding to the tract of Lissauer (p. 849), and the spinal nucleus as an extension upwards of the substantia gelatinosa of Rolando

whose cells, as we have seen, give rise to the late spino-thalamic tract.

The *motor root* fibers arise from a nucleus in the upper part of the pons underlying the lateral wall of the floor of the 4th ventricle. The nucleus receives fibers from the corticobulbar tract of the opposite side and also probably from the same side. The motor root after its emergence from the brain travels peripherally with the sensory root and, passing deep to the Gasserian ganglion, joins the mandibular (3rd) division of the trigeminal nerve to supply the muscles of mastication (temporalis masseter and pterygoids).

The *mesencephalic root* consists of a small bundle of fibers which run in company with the fillet of the motor root. Entering the pons they ascend to the *mesencephalic nucleus* of the trigeminal, an elongated mass of gray matter extending from the level of the motor nucleus to the upper region of the mid-brain. It was thought at one time that the mesencephalic root and nucleus were motor in function, but it is now generally admitted that they are composed of afferent neurons. The nucleus is looked upon as a group of cells homologous with the Gasserian ganglion and the posterior root ganglia of the spinal nerves, but which have migrated into the brain at a very early period of phylogenetic development. It is believed by Kappers to receive proprioceptive impulses from the muscles of mastication.

LESIONS INVOLVING THE TRIGEMINAL PATHWAYS. Either the peripheral portions or the central connections of the nerve may be the seat of disease. A lesion of the nerve peripheral to the Gasserian ganglion is more likely to involve only one or two of the three divisions. Pain, loss of sensibility or parosmia, or even eruptive eruptions, over the distribution of the divisions affected, may result. Paralysis of the muscles of mastication may follow injury or disease of the mandibular division, or analgesia of the cornea with ulceration (neuropathic keratitis) may result from an affection of the ophthalmic division. Loss of sensation of taste (as well as of ordinary sensibility) over the anterior two-thirds of the tongue on the corresponding side is a common accompaniment of degenerative changes affecting the mandibular division of the 5th nerve. The taste fibers to this part of the tongue are derived from the chorda tympani branch of the facial, which travel via the lingual branch of the mandibular division of the trigeminal. The loss of taste is due to pressure upon the chorda fibers by the degenerating lingual filaments, and is, as a rule, only

ary. Taste fibers are not constituents of the nerve itself. Removal of the Gasserian ganglion, for instance, does not result in permanent loss of taste on the operated side. Degeneration of the nerve central to the ganglion may occur in cases. Lesions (e.g., tumors, vascular changes) of the pons, medulla or upper cervical cord may involve the upper sensory nucleus, the motor nucleus, the trigeminal fillet (crossed) or the bulbospinal tract of the nerve. When the motor nucleus is involved weakness of the muscles of mastication results; implication of the ascending sensory fibers, or of the main sensory nucleus in the pons, is followed by loss of the sensation of touch and the discriminative aspects of cutaneous sensibility over the same side of the face, but the retention of sensibility to pain, heat and cold. The neighboring spinothalamic tract (crossed) may suffer coincidentally with the ascending sensory fibers, when thermanesthesia and analgesia over the trunk and limbs of the opposite side combined with loss of tactile sensation over the face of the same side will result (see also p. 209). Syringomyelia extending into the upper cervical region or into the bulb (syringobulbia) is likely to cause, as a result of pressure upon the spinal tract of the nerve, dissociated sensory loss of the reverse character (loss of pain and temperature and retention of tactile sensibility). Through its central connections with other cranial nerves the afferent fibers of the trigeminal nerve mediate several reflex acts, e.g., sneezing, through its nasal branches and the connections of the sensory nucleus with the nucleus of the vagus, the oculo-cardiac reflex (p. 209) through its ophthalmic fibers and the vagus, and the winking and corneal reflexes through the ophthalmic division of the facial nerve.

The trigeminal nerve, or one of its divisions, is sometimes the seat of a severe and intractable form of pain which recurs in paroxysms (*trigeminal neuralgia*) and may be accompanied by reflex spasms of the facial muscles (*tic douloureux*). The cause of the affection is unknown. In treating the condition, injections of alcohol into the division of the nerve involved are sometimes employed. An injection is made into the nerve at the infra-orbital foramen or foramen rotundum in the case of involvement of the maxillary division, and at the foramen ovale of the sphenoid or at the supraorbital notch, respectively, in disease of the mandibular division. Injections into the ganglion itself, or section of the sensory root before it enters the ganglion, is more likely to be followed

by permanent relief. The attempt is frequently made to sever the fibers entering into the constitution of the maxillary and mandibular divisions only, leaving those of the ophthalmic division, which is rarely affected, intact. The object of sparing the latter division is to obviate the corneal lesions which may result from degeneration of its fibers. The greater proportion of the fibers of the former two divisions are segregated upon the under aspect of the sensory root.

The facial nerve

The facial nerve consists of a large *motor* and a small *sensory* portion. The two portions or roots appear at the lower border of the pons and enter the internal auditory meatus in company with the auditory nerve.

The *sensory portion* of the facial, which is also known as the *nervus intermedius of Wrisberg*, contains not only afferent fibers but secretory and vasodilator (parasympathetic) fibers as well. The sensory fibers arise from the cells of the genicular (geniculate) ganglion (fig. 365). The peripheral processes of these cells are distributed through the chorda tympani branch of the facial nerve to the taste buds and mucous membrane of the anterior two-thirds of the tongue, and through the great superficial petrosal nerve and the sphenopalatine ganglion to the mucosa of the soft palate and posterior part of the nose. The chorda tympani branch joins the trunk of the lingual nerve through which it is conveyed to the floor of the mouth.² Deep sensibility (pressure pain) from the facial muscles is also, according to Loyal Davis, conveyed by afferent fibers which are distributed with the motor fibers but pass centrally in the *nervus intermedius*. The central processes of the ganglion cells end in the *sensory nucleus* situated in the upper part of the tractus solitarius. Fibers arise from the latter and ascend in the medial fillet of the opposite side to reach the thalamus (anterior nucleus). From here the pathway for taste impulses is continued by tertiary neurons to the

² The *nervus intermedius*, the genicular ganglion, the chorda tympani and part of the great superficial petrosal nerve are sometimes grouped together under the name *glossopalatine nerve*. The origin and distribution of the secretory and sensory fibers of which this nerve is composed are closely similar to those of the glossopharyngeal, and it is considered by some as an aberrant part of the latter nerve.

A small proportion of taste fibers may take an alternative route, namely, via the chorda tympani to the otic ganglion and thence by way of the internal sphenoidal and great superficial petrosal nerves, genicular ganglion and *nervus intermedius* to the brain stem (Schwartz and Weddell).

cortex of the hippocampal gyrus in the region of the uncus.

The *parasympathetic fibers* arise from the *superior salivary nucleus* (p. 942) which lies in close relation to the motor nucleus of the facial. Secretory and vasodilator fibers pass via the great superficial petrosal nerve to the sphenopalatine ganglion from where they are relayed to the lacrymal gland, and to the vessels and glands of the palate and posterior part of the nose. The secretory and vasodilator fibers to the submaxillary and sublingual glands leave the facial with the taste fibers in the chorda tympani branch.

The *motor part* of the facial is conveyed through the facial canal of the temporal bone to the stylomastoid foramen. After its emergence from the latter it is distributed to muscles of the face, auricle, and forehead. The motor fibers arise from a nucleus in the lower part of the pons and pass backwards to the lower end of the nucleus of the abducent nerve. They then ascend behind this nucleus and arching over it pass downwards and forwards to their point of emergence from the brain. As the fibers pass upwards behind the abducent nucleus they form a prominence in the floor of the 4th ventricle, known as the *facial colliculus*.

Connections; the motor nucleus of the facial nerve receives:

(a) Fibers from the cortico-bulbar tract of the same and of the opposite side.

(b) Fibers from the lateral, trigeminal and medial lemnisci, and from the spinothalamic tracts. Through these connections reflex facial movements in animals may be initiated from various receptive areas of the body.

FACIAL PARALYSIS. The effects of interruption of the facial pathway vary in certain important features according to the level at which the injury occurs. The nature of the motor loss following a lesion of the supranuclear fibers is described on page 863. In the paralysis resulting from injury to the trunk of the facial nerve all the muscles of the affected side of the face are completely paralyzed. The subject is unable to close the eye owing to paralysis of the orbicularis oculi, or to frown; the eyebrow droops. The mouth is drawn over to the sound side by the unparalyzed muscles and, unlike the paralysis in hemiplegia, the muscles of the affected side do not take part in the facial expression of emotional states, e.g., laughing or crying.

Facial paralysis may result from a lesion involving:

(a) The motor nucleus or the intra-pontine course of the motor fibers (tumors, hemorrhage, etc.).

(b) The nerve as it crosses the posterior fossa of the skull to reach the internal auditory meatus, as in fractures of the skull or tumors in this situation; the sensory portion and the auditory nerve are commonly involved as well, when loss of the sensation of taste over the anterior two-thirds of the tongue, and deafness on the affected side will result.

(c) The nerve in its course through the temporal bone as in fracture of the skull or in otitis media; inflammation of the nerve within the facial canal (aqueduct of Fallopius)—*Bell's palsy*—may occur.

(d) The nerve after its emergence from the stylomastoid foramen, as it lies behind the angle of the jaw; inflammation, parotid tumors, or accidental injury may implicate the nerve in this situation.

The glossopharyngeal nerve

The glossopharyngeal nerve contains motor, secretory, vasodilator and sensory fibers. The nerve emerges in three or four filaments from the side of the upper part of the medulla in the groove between the olive and the restiform body. The motor fibers are distributed entirely to the stylopharyngeus muscle. The secretory and vasodilator fibers (via its tympanic branch, the great superficial petrosal nerve and the otic ganglion (p. 942) supply the parotid gland. The sensory fibers arise from cells in the jugular (superior) and petrous (inferior) ganglia. The peripheral processes of the ganglion cells supply the taste buds of the posterior third of the tongue and the mucosa of the pharynx and posterior part of the mouth. The central processes terminate in the dorsal nucleus of the vagus and in the lower part of the *tractus solitarius*. Fibers (secondary neurons) pass from the latter nucleus and, crossing to the medial fillet of the opposite side, ascend to the thalamus, from where axons of tertiary neurons pass to the cortex of the hippocampal gyrus. The motor fibers arise from the upper part of the *nucleus ambiguus* situated in the reticular formation of the medulla. Secretory fibers are the axons of cells lying in the *inferior salivary nucleus* which lies below the superior nucleus of the same nerve.

The vagus nerve

The vagus nerve contains motor, secretory, vasodilator and sensory fibers. The secretory and vasodilator fibers are the fibers to the involuntary muscle of the bronchi, heart, esophagus, stomach,

small intestine, gall-bladder, etc. (parasympathetic fibers, p. 942) arise from cells in the *dorsal nucleus* (principal autonomic nucleus). This gray mass extends upwards from the lower, closed part of the medulla to beneath the floor of the 4th ventricle at the level of the striae medullares. The voluntary motor fibers arise in close relationship with the motor fibers of the glosso-

geus), and to most of the muscles of the soft palate and larynx. The cell bodies of the *sensory fibers* lie in the jugular ganglion (ganglion of the root) and ganglion nodosum (ganglion of the trunk). The peripheral processes of these cells convey impulses from the lungs, heart, larynx, pharynx, esophagus, stomach, small intestine and gall-bladder. They also innervate the taste buds

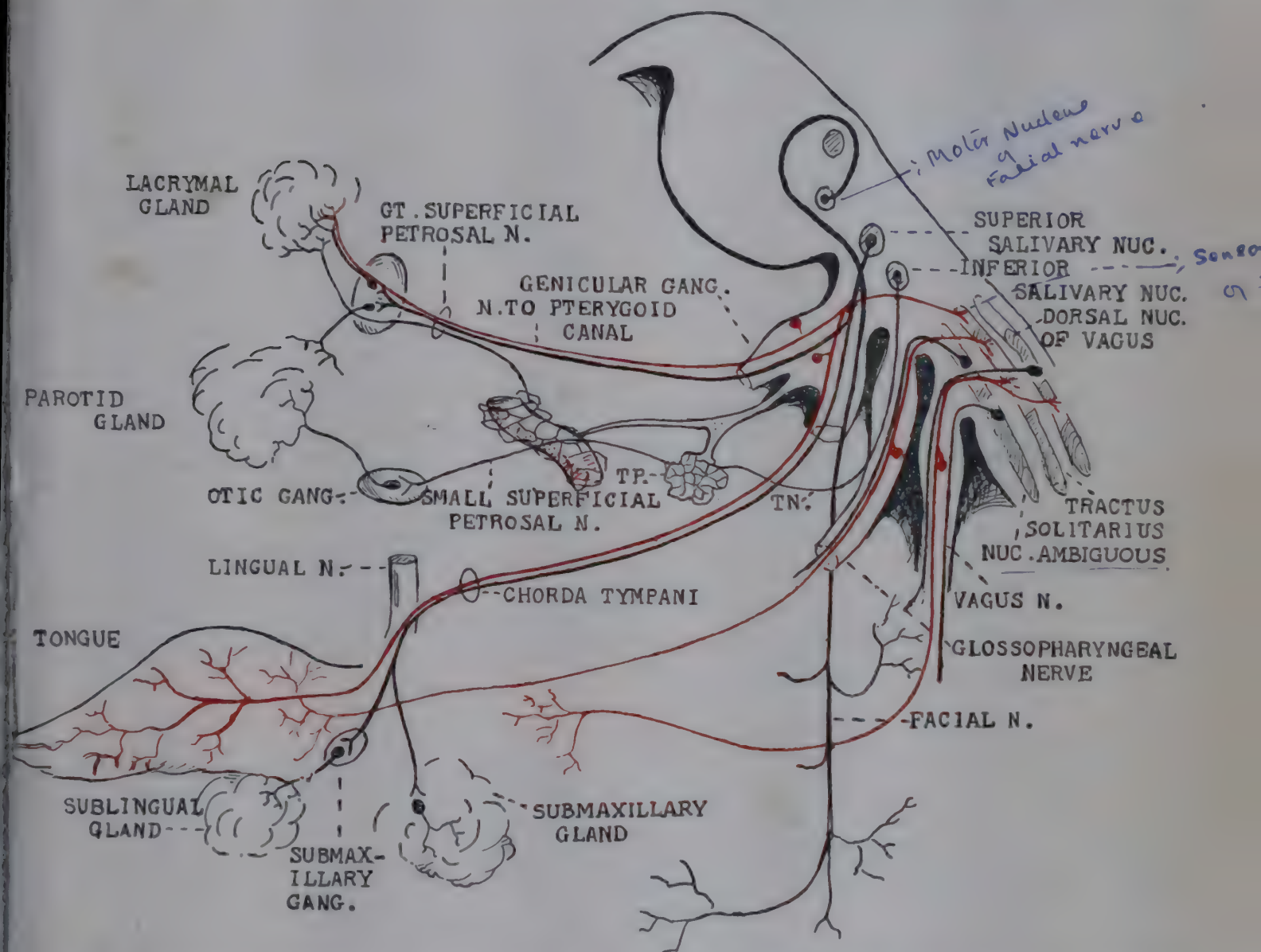


FIG. 365. Diagram to show the central connections of the facial, glossopharyngeal and vagus nerves, and the course of the secretory fibers to the salivary and lacrymal glands. Efferent paths, black; afferent paths, red. T.P., tympanic plexus; T.N., tympanic nerve. Taste fibers to the tongue are conveyed in the chorda tympani and glossopharyngeal nerves, but a small area in the region of the epiglottis receives taste fibers through the vagus. The petrous (inferior) ganglion of the glossopharyngeal and the ganglion nodosum of the vagus are not shown in the diagram.) Erratum; *ambiguous* should be *ambiguus*.

pharyngeal, namely, from the cells of the *nucleus ambiguus* lying below the glossopharyngeal neurons. They supply (through the superior pharyngeal branch) the cricothyroid and arytenoid muscles of the larynx, and the inferior constrictor of the pharynx. The pharyngeal and recurrent pharyngeal branches of the vagus also convey voluntary motor fibers derived from the bulbar nucleus of the accessory nerve (see below) to the pharyngeal muscles (with the exception of the stylopharyn-

of the epiglottis and valleculae (the depressions lying at the sides of the fold running from the epiglottis to the base of the tongue). The taste fibers terminate centrally around cells in the lower extremity of the tractus solitarius. These impulses are relayed upwards along the same paths as those conveying other taste impulses. Afferent vagal fibers from all other structures terminate in the dorsal nucleus. This latter is, therefore, both motor and sensory in function and constitutes an

important visceral reflex center. It contains the cardio-inhibitory and vomiting centers.

The accessory nerve

The accessory (spinal accessory) nerve is entirely motor and is made up of a bulbar and a spinal part. The *bulbar part* arises from the lower end of the nucleus ambiguus from cells situated below those which give origin to the motor fibers of the vagus. The bulbar fibers join the vagus in the jugular foramen and are distributed, as already mentioned, in the pharyngeal and recurrent branches of the latter nerve; these fibers of the accessory nerve innervate the muscles of the larynx, with the exception of the cricothyroid, the

glossus muscles, and the intrinsic muscles of the tongue.

THE PATHWAYS FOR VOLUNTARY MOTOR IMPULSES

The pathway taken by an impulse in passing from the cerebral cortex to a muscle innervated by a spinal nerve consists of two sections: the upper motor neuron, i.e., a cell of the motor cortex and its axon which, of course, reaches the muscle via a ventral root and a spinal nerve.

The corticospinal fibers pass from their origin (Betz cells of the motor area of the cerebral cortex, p. 887) through the white matter of the hemisphere. Converging as they descend they meet together with fibers ascending to the corpus callosum, forming here a fan-like structure known as the *corona radiata*. The pyramidal fibers then stream through the corpus striatum forming here a compact bundle known as the *internal capsule*. In the midbrain they occupy, on each side, the middle two-fifths of the base of the cerebral peduncle. In their descent through the pons they become broken up into several smaller bundles by the fibers of the pontine nuclei, but are collected together again at the lower level of the pons and continued downwards as a rounded column (the pyramid) on the ventral aspect of the medulla. At the lower end of the medulla the tract divides into two bundles of unequal size. The larger one (the crossed pyramidal tract) contains four-fifths of the total number of fibers and decussates with the corresponding bundle of the opposite side. The smaller bundle descends uncrossed (the direct pyramidal tract, see p. 855).

The corticospinal part of the pathway is considered as the *upper motor neuron*, the anterior horn cell and its axon as the *lower motor neuron* (see p. 855). The manner in which the upper and lower motor neurons are connected, and the convergence upon them of impulses from higher levels, e.g., red nucleus, superior colliculus, labyrinth, cerebellum, have been touched upon in the account of the sensory tracts in the cord. The motor neuron as a part of the reflex arc has been dealt with in Chapter LXV.

The fibers passing from the lower part of the motor area of the cortex to the cranial motor nuclei constitute the *corticobulbar tract*. This has precisely the same relationship to the cell of origin in the cerebral cortex as does the corticospinal

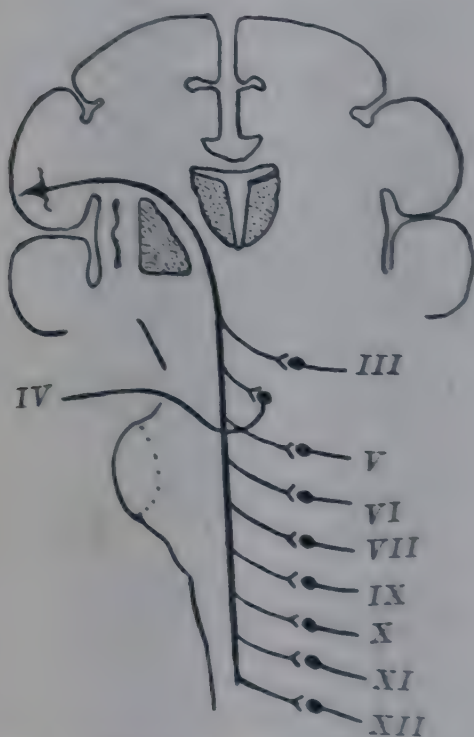


FIG. 366. Diagram of the motor nuclei of the cranial nerves and their cortical connection (in part after Ranson).

muscles of the pharynx and those of the soft palate, with the exception of the tensor veli palatini (which is supplied by the 5th nerve). The *spinal part* is composed of the axons of a group of cells in the anterior gray column of the cord extending from the 1st to the 5th or 6th cervical segment inclusive. These fibers supply the sternomastoid and trapezius muscles.

The hypoglossal nerve

The hypoglossal nerve is also purely motor. Its fibers are derived from a nucleus situated near the mid-line in the floor of the fourth ventricle and medial to the nucleus ambiguus. It supplies the thyrohyoid, styloglossus, hyoglossus and genio-

the anterior horn cells of the cord. The corticospinal fibers, however, cross at various levels throughout the brain stem. (See fig. 366.) The nuclei of the motor cranial nuclei are, of course, the motor neurons of the pathway from the cerebral cortex to the muscles of the face, tongue, larynx, etc.

THE INTERNAL CAPSULE

In a horizontal section of the cerebrum, the internal capsule is seen as a compact band of white matter lying between the thalamus and the caudate nucleus on its inner aspect and the lentiform nucleus on its lateral aspect (cf. fig. 367). In addition to the corticospinal and corticobulbar tracts, the following descending and ascending tracts compose it:

Descending:

Frontopontine tract, from frontal lobe (premotor cortex, p. 888) to pontine nuclei.

Temporopontine tract, from temporal lobe to pontine nuclei.

Corticorubral tract, from frontal lobe to the substantia nigra.

Frontothalamic tract, from frontal lobe to the nucleus of the thalamus.

Corticostriate fibers, from the premotor area to the caudate nucleus and, possibly, to the globus pallidus.

Ascending:

Thalamofrontal tract—fibers from the lateral anterior thalamic nuclei to the frontal cortex.

Thalamic radiation—fibers passing from the nucleus of the thalamus to the somesthetic post central convolution).

Auditory radiation—fibers passing from the geniculate body to the superior temporal convolution.

Optic radiation—fibers passing from the lateral geniculate body to the occipital lobe (calcarine area).

Rubro cortical fibers.

The internal capsule is bent to form a convexity medially. The region of the angle so produced is called the knee (genu). The portions in front and behind the knee are referred to as the anterior and posterior limbs, respectively. The anterior limb is between the caudate and the lentiform nuclei, the posterior limb between the thalamus and the lentiform nucleus. The anterior limb is occupied by the frontopontine, thalamofrontal, frontothalamic tracts and corticostriate fibers. The knee and anterior three-fourths of the posterior limb transmit the corticobulbar and corticospinal tracts, the former lying in front of the latter. The fibers of the corticospinal tract are divided into groups correlated with different mus-

cular regions, those carrying impulses to the upper parts of the body being placed anterior to groups innervating the lower limbs, and those controlling the proximal muscles of a given limb in front of those governing the more distal muscles.

The remainder of the posterior limb of the internal capsule is occupied by the temporopontine tract and the thalamic, auditory and optic radiations in this order from before backwards. The position of the cortico-rubral tract will be seen from figure 367.

A COMPARISON OF THE EFFECTS PRODUCED BY INJURY TO THE UPPER AND LOWER MOTOR NEURONS, RESPECTIVELY

The effects following interruption of conduction over the upper motor neuron differ in a characteristic fashion from those resulting from injury or disease of the lower motor neuron.

Disease or injury of the upper motor neuron

The following is a summary of the characters of a paralysis resulting from a lesion of the upper motor neuron (corticospinal pathway):—

(1) Hypertonia (spasticity) of the paralyzed muscles.

(2) Exaggeration of tendon reflexes, knee jerk increased, ankle clonus present.

(3) Positive Babinski response (p. 872).

(4) No permanent wasting, except as a result of prolonged disuse.

(5) Absence of the reaction of degeneration.

The corticospinal pathway is most commonly injured as the result of a vascular lesion, hemorrhage or thrombosis (usually of a lenticulo-striate branch of the middle cerebral artery) within the internal capsule. The lesion is usually unilateral and its effects involve the muscles on the opposite side of the body. The condition is termed *hemiplegia*. After the state of shock, which lasts for a variable number of days following the injury, has passed off, the following features are observed:

(1) **LOSS OR IMPAIRMENT OF VOLUNTARY POWER**, involving the muscles of limbs, trunk and face of the opposite side is evident. There is often little or no actual paralysis, merely a muscular weakness (paresis). The finer movements, such as those of the hands and fingers are especially affected. The volitional movements of the lower part of the face are involved to a greater degree than those of the upper, e.g., raising the eyebrows and closure of the eyelids, the reason being, very probably, that the part of the facial nucleus governing the latter movements receives fibers from both hemispheres. When voluntary efforts are made to

move the lower part of the face, as in showing the teeth, or pursing the lips, marked impairment of muscular power may be evident, yet emotional expressions, e.g., laughing, smiling or crying, though involving the same muscles may show little departure from the normal. For example, the patient, though unable to raise the corner of his mouth when asked, may smile naturally a moment later. The impulses which bring about movements of the facial muscles in these more automatic movements of facial expression apparently travel by other than pyramidal pathways (p. 874).

(2) MOVEMENTS OF THE JAW, TONGUE AND SOFT PALATE on the opposite side to the pyramidal lesion show some weakness but since they are

electrical reactions (p. 780) are normal also the premotor area of the cortex (LXIX.)

(4) REFLEXES. The tendon jerks at knee and elbow are exaggerated on the hemiplegic side and there may be ankle clonus. The response is "Extensor" in type¹ the abdominal cremasteric reflexes (p. 873) are abolished.

The upper motor neuron may be injured by injury or disease (hemorrhage, tumor) at any part of its course from the cerebral cortex to the spinal centers. The effects, though varying in degree, are the same as those described above. The general features just described, e.g., impairment of muscular power, hyperreflexia, exaggerated reflexes, present certain

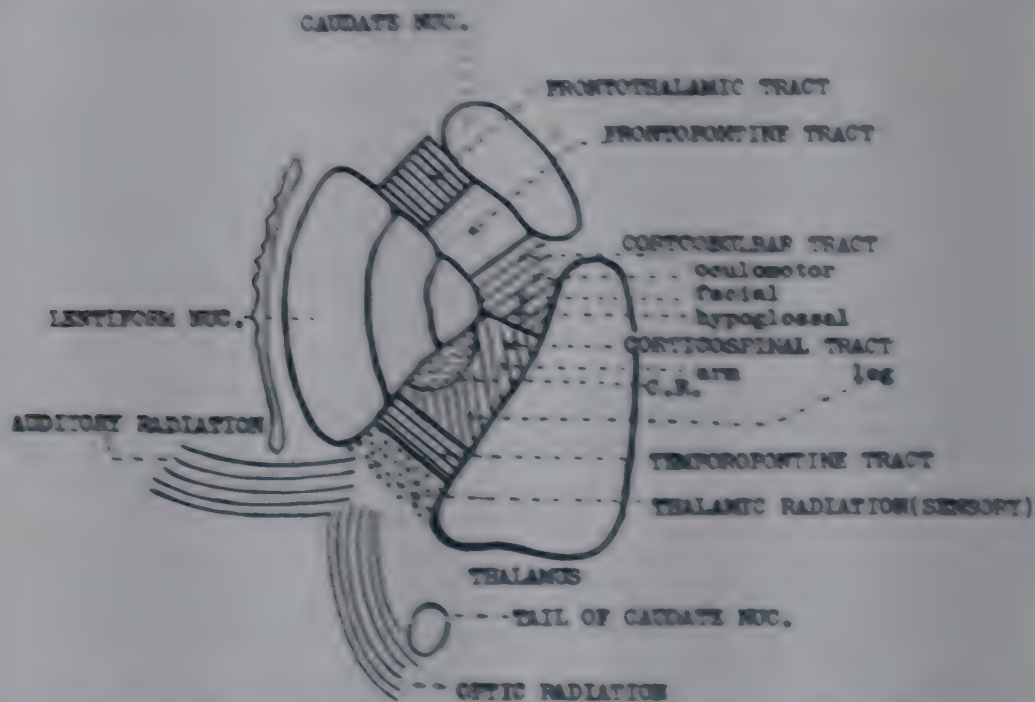


FIG. 367. Diagram of the internal capsule. C. R. = corticobulbar tract.

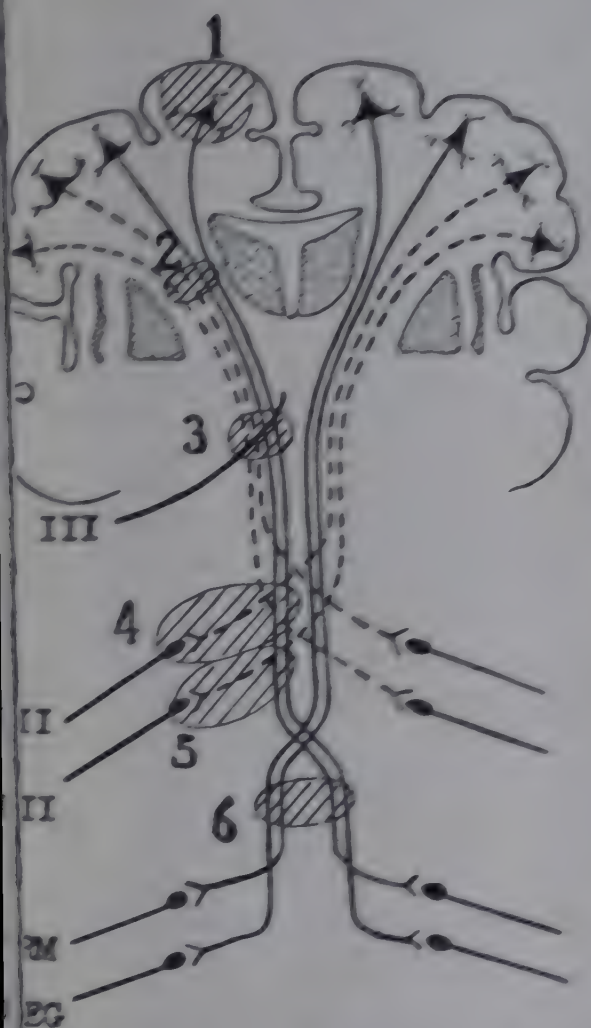
bilaterally innervated this, as a rule, is not pronounced. There may be some deviation of the jaw upon opening the mouth, and of the tongue when protruded, to the hemiplegic side. The soft palate is lower on the hemiplegic side and the uvula tends to be drawn away from this side (i.e., toward the side of the cerebral lesion).

(3) HYPERTONIA OF THE MUSCLES—SPASTICITY. This involves on the paralyzed side the flexors of the elbow, wrist and fingers, adductors of the shoulder and pronators of the forearm. In the lower limb the extensors of the hip and knee, the adductors of the hip and the plantar flexors of the ankle are hypertonic. The attitude resulting from this distribution of the hypertonia has been compared to the decerebrate rigidity of animals (p. 824). The muscles do not waste and the

peculiar to the level of the lesion. The latter implicates the tract where, as in the internal capsule, the fibers form a compact bundle. The peripheral effects are likely to be more variable, i.e., to be *hemiplegic*, than when the lesion is in the cerebral cortex or the corona radiata. Then the paralysis tends to be more localized. It may affect only one limb—*monoplegia*—when the lesion interrupts the fibers of the corticospinal tract above the nuclei of the motor cranial nerves (supranuclear lesion) the muscles innervated by the latter will, of course, be involved as well as those above with the muscles of the limbs. The fibers from the cortex to the spinal centers cross at different levels but all above the level of the corticospinal fibers. If,

¹ This is in reality a flexor reflex (see p. 874).

involves the pyramidal pathway below, say, for the seventh cranial nerve but above decussation of the corticospinal fibers the lesion will involve the limbs and trunk of the opposite side and perhaps those of the tongue, face and throat, but the facial muscles will be spared. When the lesion involves the facial



3. Diagram illustrating the effects of lesions at different levels. 1, lesion of cortex causing monohemiplegia, depending upon its extent; 2, lesion of internal capsule, hemiplegia; 3, lesion of midbrain involving pyramidal fibers and nucleus of third nerve (Weber's paralysis); 4, lesion in pons involving pyramidal fibers and nucleus of facial nerve, hemiplegia with homolateral facial paralysis; 5, lesion in medulla involving pyramidal fibers and nucleus of hypoglossal nerve, crossed hemiplegia and homolateral paralysis of lingual muscles; 6, transection of spinal cord, paraplegia. (In part from Volzger and from Ranvier.)

nerve together with the pyramidal tract, hemiplegia results. This is paralysis of the limbs and trunk of the spastic type on the opposite side to the lesion, together with the paralysis of the lower neuron type on the same side to the lesion. Similarly, the hypoglossal may be involved together with the pyramidal tract above its decussation. Wasting and

paralysis of the tongue muscles on the same side as the lesion, and spastic paralysis of the limbs on the opposite side will result. Again, the glossopharyngeal nucleus may be implicated with consequent paralysis of the stylopharyngeus and loss of sensation over the posterior third of the tongue. The oculomotor nerve nucleus, since it lies in close proximity to the pyramidal tract, is also sometimes involved with the latter. The level of the lesion would then be indicated by paralysis of the ocular muscles innervated by the third nerve on the side of the lesion and hemiplegia on the opposite side. This is known as Weber's paralysis (fig. 362).

It is evident that the paralysis is more likely to be bilateral if the lesion is situated in a region where, as in the brain stem or spinal cord, the corticospinal tracts of the two sides are approximated, than if it is located at a level where these tracts are widely separated, as in the corona radiata or internal capsule; then unilateral effects are usual. Injury to the crossed pyramidal tract on one side of the cord, should it occur, will result in paralysis of the muscles on the same side. Complete interruption of both pathways in the cord will of course result in paralysis on both sides of the body below the level of the lesion—paraplegia (p. 870).

LESIONS OF THE LOWER MOTOR NEURON

Destruction of the motor cells situated in the anterior horns of the cord or of the motor nuclei of the cranial nerves, of the anterior spinal nerve roots or of the peripheral nerve trunks, results in complete paralysis of the muscle fibers supplied by the injured neurons. The paralysis is of the flaccid type, of which the following are the main clinical features.

- (1) Muscular hypotonia.
- (2) Loss of tendon reflexes.
- (3) Atrophy (wasting) and degeneration of muscles.
- (4) Electrical reaction of degeneration (p. 780).

The flaccid paralysis does not, as in lesions of the upper neuron, show a hemiplegic distribution. When the lesion involves the anterior horn cells as in anterior poliomyelitis, or the anterior roots of the spinal nerves, the paralysis assumes a segmental pattern. Individual muscles or scattered groups of muscles are commonly involved. Injury to the anterior horns usually results in a bilateral paralysis, though different muscles on the two sides of the body may be affected. Furthermore, since a given muscle receives its innervation from

more than one spinal segment, and conversely a single spinal segment supplies parts of several muscles (p. 848), a localized lesion of the cord may result in the paralysis of fibers scattered throughout several muscles, leaving other fibers in the same muscles intact. Weakness rather than complete paralysis of certain muscles will result. Even when the lesion involves several spinal segments, the muscles innervated by those at the upper and lower limits of the spinal region involved, will show partial paralysis, since they will still be supplied by undamaged nerve fibers from adjacent healthy segments.

The entrance of the ventral roots into the formation of the brachial and lumbar plexuses is accompanied by a regrouping of their constituent fibers which are continued into the various peripheral nerve trunks. A lesion of a peripheral nerve, therefore, produces a paralysis which is non-segmental in character. It corresponds to the distribution of the muscular branches of the nerve.

Cutaneous sensory loss will show a segmental pattern when the posterior roots of the spinal nerves are involved, but when the peripheral nerve trunk is implicated the distribution of the sensory defect will conform to that of the cutaneous branches of the nerve (see also figures 358 and 359). Injury to the ascending tracts in the cord will, of course, cause sensory loss below the level of the lesion (p. 851) and will vary in kind according to the particular fibers which have been interrupted.

FUNCTIONAL, MORPHOLOGICAL AND CHEMICAL CHANGES IN DENERVATED MUSCLE

A lesion involving any part of the lower motor neuron—anterior horn cell or axon—such as may result, respectively, from poliomyelitis or peripheral nerve injury, is followed by degenerative changes which extend to and include the nerve terminals within the muscle. A muscle thus completely denervated exhibits constant, fine, rapid, rhythmical contractions. This so-called fibrillation of the denervated muscle does not appear until several days after the abnormal electrical reactions (reaction of degeneration, p. 780) have already developed and complete degeneration of the nerve has occurred. The muscle fibers contract asynchronously; the contractions involve only a part of the length (0.5 to 1 mm.) of the fiber and give rise to small irregular action potentials. The fibrillation can sometimes, though not commonly, be seen through the skin. Having once appeared, fibrillation persists for a year or more and until the contractile elements have undergone complete atrophy. According to

Denny-Brown, a reduction in tension develops in the muscle when stimulated maximally can be detected within 2 minutes after section of the nerve, but investigators have been unable to observe any loss of contractile force until after a much longer interval (30–40 hours). An outstanding functional effect of denervation is the great increase in the sensitivity of the muscle to the intravenous or intra-arterial injection of acetylcholine. Normal muscle is excited by an intra-arterial injection of from 0.2 to 2.0 mg. of acetylcholine, whereas denervated muscle responds to a dose of from 0.002 to 0.02 γ . It is generally believed that this hypersensitivity to acetylcholine is responsible for the Vulpian and Sherrington effects, and most probably also for the "fright reaction" described by Bender (p. 947). The denervated muscle is hyperexcitable, though to a less pronounced degree than to potassium chloride.

The denervated muscle soon commences to atrophy, a reduction in its bulk becoming apparent within a few days after section of the nerve. Atrophy progresses rapidly and is followed by degeneration of the contractile elements. Microscopic changes in the muscle fibers consist of swelling and vesiculation of the myofibrils, a reduction in sarcoplasm, and fading, followed by the disappearance of the striations of the myofibrils. Ultimately all contractile tissue disappears and is replaced by fibrous tissue and fat. As these morphological changes are occurring, the muscle gradually loses its plastic or ductile quality, flexors and adductors shorten and become more or less "set" in their positions. The antagonistic muscles lengthen correspondingly. This state of the muscles is called *contracture*.

The chemical changes in denervated muscle consist of a reduction in glycogen, phosphocreatine and adenosinetriphosphate, but they do not become pronounced until the onset of fibrillation. The breakdown of glycogen and subsequent resynthesis of glycogen by the denervated muscle during a work period is normal for a few days following nerve section but when fibrillation supervenes the ability of the muscle to restore its glycogen stores after contraction is greatly impaired. The atrophic muscle shows a large increase in calcium, a small increase in chloride, and a decrease in potassium. Changes in chloride and potassium can be accounted for by the reduction in muscle mass and its replacement by interstitial tissue. The increase in calcium is great, however, to be explained entirely in this way.

The cause of fibrillation in denervated muscle is unknown, but it is not improbable that it is a manifestation of its hypersensitivity to acetylcholine. The observation of Magladery and Solandt that quinine, which abolishes acetylcholine hypersensitivity, suppresses fibrillation is highly suggestive; yet Auer and his associates have shown, direct stimulation of denervated muscle does not cause the release of acetylcholine. It follows, therefore, that if the stimulant effect of this agent is responsible for fibrillation, the agent must be carried to the muscle in the blood stream.

ased sensitivity to acetylcholine may be due to a of cholinesterase for, according to Marnay and hmansohn, this enzyme, which normally is con- cated in the neighborhood of the nerve endings in tal muscle, disappears after denervation. The of cholinesterase might also explain the failure of pe to cause anything more than a transient aug- mentation of fibrillation.

ge atrophy following nerve degeneration has not explained satisfactorily. Langley and Kato ved that the ceaseless activity of the fibrillating le was the primary cause, thus attributing it to work and exhaustion. Though other investigators incline to this view it has not received general tance. One reason for questioning this explana- is that the tension developed by the fibrillating le is less than that of the ordinary tonic contraction rmal muscle, yet the oxygen consumption of the vated muscle is greater than that of normal ols. One would not expect atrophy to result r such conditions. There is little evidence for the r belief in trophic nerves in the original meaning e term, namely, that certain nerve fibers exerted a ic nutritional or trophic control over the muscle. e sense that denervation is followed, among other s, by profound nutritional changes in the muscle, he motor nerves do serve a trophic function, but a function is thought to be secondary or incidental an than constituting a direct and essential action the muscle fiber.

SECTION OF THE CORD. BROWN-SÉQUARD'S Syndrome . PARALYSIS

esion which completely interrupts the con- y of one-half of the cord causes the following hances:

I. Motor paralysis

per neuron type of paralysis of the muscles the level of the lesion and on the same side s as a result of the severance of the cortico- tracts. The muscles supplied by the seg- actually implicated in the lesion will, as a of destruction of the anterior horn cells, t a flaccid paralysis (lower motor neuron The flaccid paralysis is, however, small in unless the lesion involves the cervical or r enlargements (fig. 369).

II. Vasomotor paralysis

a result of the interruption of pathways in lateral funiculus connecting the vasomotor with the spinal sympathetic centers (cells al horn) dilatation of the cutaneous vessels and on the side of the lesion occurs. The of the paralyzed side is at first redder and

warmer than normally; later it becomes cyanosed and cold.

III. Sensory changes

(a) *Sense of position and movement and of tactile discrimination* (compass test), being mediated by fibers of the posterior funiculus which do not cross, are lost below the level of and on the same side as the lesion. The loss of the sensations from the muscles and joints causes ataxia on the side of the lesion. The non-sensory impulses from the muscles since they pass to the cerebellum by two paths (direct and indirect spinocerebellar) are not completely interrupted on either side. The partial blocking of these impulses, however, contributes to the ataxia.

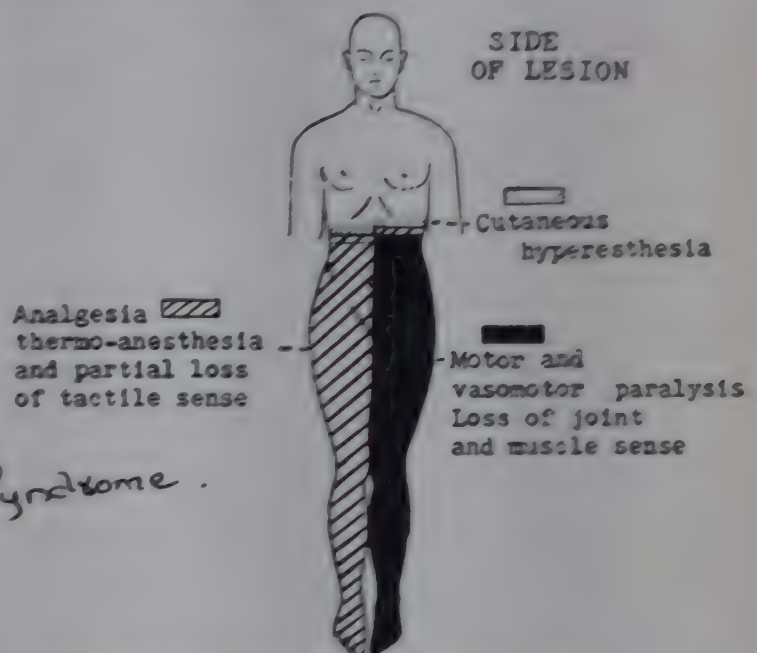


FIG. 369. Diagram showing effects following hemi-section of the cord in the lower thoracic region.

(b) *Painful and thermal sensations* are conveyed by fibers which cross shortly after their entrance into the cord (lateral spinothalamic tract). As a result of the destruction of these fibers before their decussation, a narrow zone of skin at and just below the level of the lesion and on the same side, shows analgesia and thermoanesthesia. The rest of the body below the lesion and on the same side shows no such loss, but as a result of the destruction of fibers after crossing, pain and temperature are completely lost on the opposite side. Owing to this fact, that some fibers mediating these sensations ascend for a segment or two before crossing, the appreciation of pain and temperature is retained in a zone on the contralateral side just below the lesion. This zone corresponds in extent to that of analgesia and thermoanesthesia on the homolateral side.

(c) *Touch and tactile localization.* It has been pointed out (p. 853) that fibers mediating these sensations cross at different levels in the cord. Therefore, a unilateral lesion of the cord interrupts fibers which have crossed from the opposite side of the body as well as those ascending from the same side, i.e., uncrossed fibers of the posterior columns. These sensations on the side of the lesion are still mediated, however, by fibers which have escaped destruction through having crossed below the lesion to the ventral (anterior) spinothalamic tract of the uninjured side; while those from the side opposite to the lesion are carried by the fibers of the posterior columns of that side. The sensations of touch and tactile localization, therefore, are not lost on either side of the body as a result of a unilateral lesion of the cord, though some impairment on the same side as the lesion may be detected. A narrow zone above the lesion on both sides is hypersensitive to touch, pain and thermal stimuli (hyperesthesia). This is probably an irritative phenomenon; it is usually transitory.

SYRINGOMYELIA

This commences as a proliferation of neuroglia (gliosis) in the spinal gray matter. The newly formed tissue breaks down with the formation of cavities filled with a gelatinous material. The process may extend for considerable distances up and down the cord. The starting point of the disease is most frequently the base of the posterior gray column. The lower cervical and upper thoracic regions are most commonly affected. The disease may extend into the bulb (syringobulbia) when signs of implication of the cranial nuclei appear.

Dissociated sensory loss and muscular weakness with a segmental distribution are among the characteristic features of the disease. Owing to the site of the changes, the fibers mediating pain, heat and cold, where they make connections with the cells of the posterior horns, are first destroyed. If the lesion is unilateral, thermoanesthesia and analgesia of the skin supplied by, and on the same side as the diseased segments result. Other sensations, e.g., touch, muscle sense, are unaffected until later in the disease. Involvement of the spinal nucleus of the trigeminal results in the characteristic sensory loss over the face, the areas supplied by the ophthalmic, maxillary and mandibular divisions being affected successively in this order (p. 858). When both dorsal horns are involved, or as a result of expansion of the cavity the anterior gray commissure is pressed upon and the fibers injured at their point of crossing, the thermoanesthesia and analgesia are bilateral. The muscles innervated by the diseased segments become weak and wasted; these effects often appear first in the small muscles of the

hand. So long as the disease does not cause injury to the white matter, the sensory and motor effects are limited and have a segmental distribution. Involvement of the corticospinal tracts will result in spasticity below the level of the lesion, while pressure upon the spinothalamic tracts and dorsal columns will be followed by sensory loss below the level of the lesion. The degree of sensory loss, its type and distribution and whether homolateral or contralateral vary according to the extent to which the individual tracts are affected by the disease. As a result of the loss of the protective sensations (pain and temperature), subjects of syringomyelia are prone to suffer injuries which, not being perceived at the time, are neglected and ultimately lead to serious lesions, e.g., painless disorganization of a joint (arthropathy, Charcot's joint). Involvement of the sympathetic centers in the lateral columns lead to vasomotor disturbances, excessive sweating or absence of sweating, cyanosis, etc. So-called trophic disturbances, e.g., ulcers, whitlows, gangrene, etc. are largely the result of vasomotor abnormalities and the loss of sensation which, as just mentioned, permits an injury, trivial perhaps at first, to be disregarded.

SUBACUTE COMBINED DEGENERATION OF THE CORD

This condition involves the white matter of the cord and is almost always associated with pernicious anemia. The degenerative process consists of breakdown of the myelin sheaths, subsequent destruction of the axons and their replacement by newly formed glial tissue. The changes are most pronounced in the corticospinal and cerebellar tracts and in the posterior columns. The spinothalamic tracts, as a rule, are involved to a less degree. The chief clinical features are, therefore: (a) muscular weakness and spasticity, (b) impairment of the sense of position and passive movement of the limbs with consequent ataxia and a positive Romberg sign, (c) loss or impairment of sensitivity to touch, pressure, localization, spatial discrimination, vibration, pain and temperature. The relative extent to which these sensations are lost is variable. The cutaneous sensory loss is at first of the distal regions of the extremities—hands and wrists, feet and ankles. Paresthesias (tingling, pricking and burning sensations) frequently precede the sensory loss. (d) The reflexes vary. The tendon jerks are frequently exaggerated as a result of involvement of the corticospinal tracts, but they may disappear as the disease progresses. The plantar response is usually of the "extensor" type, especially in the later stages.

The severity of the nervous manifestations does not always run parallel with that of the blood picture; neurological features may be pronounced though anemia is of mild degree, or vice versa. It is commonly stated that subacute combined degeneration of the cord may progress though the blood picture is restored to normal as a result of treatment with liver extract.

It has been shown, however, by Farquharson and Graham that if the dosage of liver extract is increased considerably above that which will keep the anemia in abeyance, the nervous condition shows marked improvement. Strauss and his associates also state that in their experience the progress of the degenerative lesion in the cord can be completely arrested by the administration of liver extract, provided that the dose is sufficient to maintain a red cell count of 4,500,000, a mean corpuscular volume of less than 100 cu. microns and a color index of 1.0 or lower.

TABES DORSALIS, LOCOMOTOR ATAXIA

In this condition, which is the result of syphilis, the fibers of the dorsal roots after their entry into the cord (i.e., the central processes of the primary sensory neurons) are attacked. The ganglion cell bodies of the dorsal roots, as a rule, are not affected. The essential lesion within the cord, therefore, involves the entrance zone of the lateral division of the dorsal roots (dorsi-lateral fasciculus of Lissauer), and the dorsal fasciculi (gracilis and cuneatus). The endogenous fibers of the cord escape, but although it is those tracts composed of exogenous fibers which are specifically attacked by the disease, the functions of the cerebellar and spinothalamic tracts are also seriously disturbed as a result of degeneration of the primary neurons leading to them. The descending tracts remain as a rule practically unaffected. The reason for the selective destruction of the exogenous fibers of the cord is unknown; possibly it is compression of the fibers by proliferation or inflammatory swelling of the meninges at the point of entrance of the posterior root. The central fibers of the trigeminal nerve which are homologous with the fibers of the posterior spinal nerve roots may also be implicated.

The sensory changes are those which might be expected to result from a gradual degeneration of dorsal root fibers.

The chief manifestations are as follows: (a) During the degenerative process paresthesias of various types, hyperesthesia and stabbing pains are common. (b) Impairment, or loss to a variable degree, of all forms of sensation follows. Loss of the sense of position and of passive movement, and blockage of afferent cerebellar impulses result in marked incoördination of the muscles—ataxia. Movements are jerky, exaggerated and imperfectly controlled, the subject being unable to move his hands and feet in the desired direction or to assume a given position at will, e.g., bringing his finger to the nose or placing the heel of one foot upon the toes of the other. The gait is ataxic, the feet are kept wide apart, raised unnecessarily high and brought down in a stamping fashion; the patient may learn to overcome this tendency by shuffling.

Involvement of sensory cranial fibers causes corresponding inoördinate actions of the facial, ocular and lingual muscles. When standing with the eyes closed the patient, being thus deprived of an important

aid in maintaining his equilibrium, tends to sway and may fall (Romberg's sign). (c) The interruption of the pathways for proprioceptive impulses from the skeletal muscles (p. 822) results in extreme *hypotonia*. (d) The *tendon reflexes* are abolished as a result of the destruction of the afferent limb of the proprioceptive reflex arc. The abdominal reflexes are present. (e) "*Lightning pains*" and *trophic disturbances*. The former are severe stabbing paroxysmal pains usually localized to an area supplied by one or more spinal segments. Vasodilatation, small hemorrhages or herpes zoster may occur in the painful area. These vascular and cutaneous effects have been attributed to antidromic impulses reaching the periphery via sensory fibers. The skin of the affected area may break down with the formation of so-called trophic ulcers. Painless destruction of joints (Charcot's joint) is not uncommon in tabes. The loss of the sense of pain which causes the patient to suffer injuries of which he is unaware, the extreme hypotonia of the muscles which normally support the joint, and the vascular disturbances resulting from damage to autonomic fibers combine to produce such joint conditions. They are usually classed among the trophic disturbances, the term implying that the interruption of trophic impulses is responsible. However, the existence of true trophic fibers, i.e., specific fibers which preside over the nutrition of the peripheral tissues, is questionable. (f) *Tabetic crises*. These are apparently the result of the involvement of afferent autonomic fibers which enter the cord by the dorsal roots. They consist of paroxysmal attacks of pain and functional disturbances in one or other of the viscera. Gastric crises are the commonest. They consist of severe epigastric pain and vomiting. *Rectal crises* consisting of pain in and increased activity of the rectum, *vesical crises* with bladder pain and difficult urination or *laryngeal crises*, in which spasm of the adductors of the larynx with dyspnea may occur. (g) *Ocular signs*. The pupils are as a rule constricted and often unequal. The Argyll-Robertson pupil (p. 1014) in which the reflex to accommodation is retained but the reaction to light is lost, is a characteristic ocular feature of tabes. The pupil also frequently fails to respond by dilatation to stimulation of the skin of the neck (cilio-spinal reflex). The loss of this reflex is usually attributed to degeneration of the central sympathetic pathway through which the dilator pupillae muscle is innervated (p. 1012). Some drooping of the upper lid (ptosis) may also result from the blockage of sympathetic pathways which normally transmit impulses to the smooth muscle in this situation; compensatory contraction of the frontalis muscle with wrinkling of the skin of the forehead results. Damage to the fibers of the 3rd, 4th or 6th nerves results in paralysis of the ocular muscles, the external rectus most commonly. Squint and double vision (diplopia (p. 1018)) are consequences. Primary optic atrophy occurs.

COMPLETE TRANSVERSE DIVISION OF THE CORD

A sudden, or rapidly progressive, complete interruption of the continuity of the cord may result from injury (e.g., gunshot wound, fracture-dislocation of the spine, etc.) or from acute inflammation (e.g., transverse myelitis). Immediate and complete loss of voluntary power below the level of the lesion results. Paralysis of both lower limbs resulting from this or any other nervous lesion is spoken of as *paraplegia*. Complete division of the cord in the lower cervical region will result in paralysis of all four limbs, *quadriplegia*. A lesion of this nature in the upper cervical region is of course rapidly fatal since the diaphragm and other respiratory muscles are isolated from the respiratory center. The subsequent history of the subject of a complete transverse spinal lesion has been divided into three stages by Riddock.

I. Stage of spinal shock

Immediately following the injury there are, complete loss of visceral and somatic sensations, and flaccid paralysis below the level of the lesion. The skeletal muscles are quite toneless. The tendon jerks, plantar response and abdominal reflexes are abolished. The cremasteric and bulbocavernosus reflexes, though absent as a rule, may at times be elicited. The anal reflex is present. A zone of heightened sensitivity (hyperesthesia) immediately above the level of the lesion is present and spontaneous pains in this region, or a feeling of tightness encircling the body may be experienced by the patient. There is retention of urine and feces due to tonic contraction of the sphincters. This stage is analogous to the state of spinal shock in lower animals but is much more severe and prolonged. In the dog or rabbit, for example, flexor reflex activity is retained and the knee jerk is elicitable within half an hour or less after spinal transection (p. 828). In man spinal shock lasts for from one to three weeks.

II. Stage of reflex activity—*paraplegia in flexion*

Recovery of the isolated spinal centers; the flexor muscles gradually regain a part of their lost tone. The first reflex to appear is the so-called extensor response or sign of Babinski. At this time the abdominal (rectus muscles) and other superficial reflexes can also usually be evoked with ease. Later the tone of the extensor muscles is restored to some extent and the tendon jerks reappear. The knee jerk returns usually in from 3 to 7 weeks after the injury and may become somewhat

greater than normal, but shows certain abnormal features. The extension of the knee is not maintained in the normal way for a brief period; instead the quadriceps after its contraction relaxes suddenly again and allows the leg to fall like a dead weight. The ankle jerks are weak or may not appear at all. Clonus is very rarely obtained. It will be recalled that in the spinal animal, though flexor reflex activity is brisk after spinal transection, extensor reflexes, apart from the knee jerk which returns promptly, are restored very slowly. "Spinal man" also shows a preponderance of the flexor reflexes. The flexor responses are, as mentioned above, well-developed before the knee jerk appears and become progressively more active, whereas, extensor responses, for the most part cannot be elicited. Stroking the skin of the sole, for example, will result in a response involving a number of flexor muscles accompanied by inhibition of their antagonists. Sometimes contraction of the extensors of the opposite limb (crossed extensor reflex, p. 819) occurs. When the stage of reflex activity is fully developed, spontaneous reflex spasms of paralyzed limbs occur and quite a mild stimulus applied to the paralyzed limbs or to the genital region results in a wide-spread reflex contraction of flexor muscles. This response, which has been called the "*mass reflex*" by Head and Riddock, will be considered more in detail presently. In this stage the bladder and rectum empty automatically. Though the tone of all muscles is lower than normal, the flexors are less hypotonic than the extensors, and the limbs tend to be drawn into flexed positions. The paralyzed state is therefore referred to as *paraplegia in flexion*. The duration of the stage of reflex activity is indefinite. The tracts whose destruction is essentially responsible for the features of paraplegia in flexion are the corticospinal and vestibulospinal. It will be remembered that the extensor dominance of the decerebrate animal is abolished, whereas flexor responses are retained and may even be increased after destruction of the vestibular nuclei.

III. Stage of failure of reflex activity

This stage is ushered in when, as a result of some infective complication (e.g., bed-sores, cystitis, pyelitis, etc.) and the consequent absorption of toxins, the spinal reflex centers are rendered functionless. As a rule it precedes death by a short interval. The extensor reflexes (e.g., knee jerk) are the first to disappear. Then the flexor

ponses are elicited with gradually increasing difficulty and the "mass reflex" does not occur. Finally all reflex activity is abolished and the muscles waste. Retention of urine and feces occurs, or there may be continual dribbling of urine, and fecal incontinence. Degeneration of the cells of the spinal gray matter, as a result simply of their isolation from higher centers (isolation dystrophy) which, according to Sherrington, occurs in the spinal monkey, does not apparently occur in spinal men for, as mentioned above, the stage of reflex activity may in the presence of infective conditions continue for indefinitely long periods. If toxemia commences in the first stage (spinal shock) this may merge into the third stage, the second stage of reflex recovery being absent.

INCOMPLETE DIVISION OF THE CORD

A bilateral lesion destroying the pyramidal tracts above the lumbar region but leaving the vestibulospinal fasciculi intact causes *paraplegia in extension*. The muscles are spastic and extensor activity predominates. The tendon jerks are exaggerated and patellar and ankle clonus can be readily elicited. Whereas paraplegia in flexion is analogous to the spinal state of animals, paraplegia in extension is more comparable to extensor rigidity. The "extensor" plantar response, which in reality a flexor protective reflex, is present, but much less intense and involves fewer muscles, than that seen in paraplegia in flexion. It is accompanied by a crossed extensor reflex. The mass reflex is absent. The abdominal reflexes are absent. Paraplegia in extension will also result from a bilateral lesion of the corticospinal tracts throughout any part of their course from the cortex downwards, and in a unilateral lesion (hemiplegia) the features are of the same nature. On the other hand, a lesion of the cord even though incomplete, if it involves the vestibulospinal tracts as well as the pyramidal, gives rise to the features characteristic of paraplegia in flexion.

The "mass reflex"

This, as already mentioned, occurs in conditions in which reflex activity predominates and when the spinal centers which had been released from higher control establish independent activity. A relatively weak stimulus causes, as a result of irradiation within the cord, a diffuse reflex response in which are included a large number of voluntary muscles as well as the musculature of certain viscera. The response shows no "local sign," i.e.,

there is no circumscribed area from which it is elicitable alone, and it shows little or no modification upon varying the site of application of the stimulus. It can be evoked from anywhere over the limbs, genital regions or abdomen below the level of the lesion. The type of stimulus to which it responds is one which would be painful or unpleasant (e.g., scratching, pinching, pricking, etc.) could it be felt by the subject. It is an exaggeration of the normal withdrawal or protective reflex (flexion reflex, p. 819). The mass reflex comprises the following reactions:

(a) A *flexor spasm* of the muscles of the abdominal wall (recti) and lower extremities as a result of stimulation of the skin of the abdomen, genital region or limbs.

(b) *Sweating* caused by stimulation of the skin or of the vesical or rectal mucosae; its distribution is, roughly, that of the sensory loss.

(c) *Evacuation of the bladder*, even though only partially full, and of the *rectum* follows stimulation of the skin, or of the respective mucous surface. Evacuation of the bladder is affected normally by contraction of the detrusor muscle and relaxation of the sphincter (p. 412). Immediately after complete section of the cord the detrusor muscle may be capable of contracting reflexly as a result of the stimulus caused by distension of the bladder wall, but inhibition of the sphincter fails to occur, and retention of urine results. When, however, the sphincter is dilated by means of a catheter, the bladder wall contracts and evacuation occurs readily. After a time, relaxation of the sphincter, as well as contraction of the detrusor muscle, occurs through the reflex center in the sacral cord, when a sufficient quantity of urine (500 to 600 cc.) has collected to distend the bladder and so act as a stimulus. This reflex which characterizes the so-called *automatic bladder* and is brought about by intravesical stimulation is very readily facilitated by extra-vesical stimuli. Thus, as mentioned above, a scratch upon the sole of the foot or in the genital region causes a spasm of flexor muscles and, even though the quantity of urine present in the bladder at the time be quite inadequate to stimulate through distension alone, the extra-vesical stimulus has such a facilitating effect upon the vesical reflex that evacuation results. The facilitation caused by an extra-vesical stimulus is always more readily demonstrable upon the detrusor contraction (i.e., when a catheter is in position) than upon the sphincter. Though they have not been studied in the same detail the mechanisms con-

cerned in the reflex evacuation of the rectum are no doubt similar.⁴

THE PLANTAR REFLEXES

This is the most appropriate place to consider these and other superficial reflexes.

The *normal plantar response* to a light scratch applied to the skin of the sole is plantar flexion of the four outer toes with no movement, or, more usually, plantar flexion of the great toe. The toe movements are accompanied by dorsiflexion of the ankle and contraction of the tensor fasciae femoris. The center for the reflex lies in the first sacral segment; its physiological significance is unknown. In a lesion of the cortico-spinal tract at any level above the first sacral segment, the normal response is replaced by one in which *dorsiflexion* of the great toe and spreading or fanning of the outer toes occurs. This response is called after its discoverer the *sign of Babinski* (fig. 370). From the dorsiflexion of the great toe, which is due to the contraction of the extensor longus hallucis, this reflex is also frequently referred to as the *extensor response*.⁵ This term, however, is incorrect since the upward movement of the great toe is part of a general flexor response homologous with the flexor reflex elicitable from the hind limb of a lower animal (p. 819). The dorsiflexors of the toes, though classed anatomically as extensors must, when compared physiologically with similar muscles in the limb of an animal such as the dog, be included among the flexors. In lesions of the corticospinal tracts (e.g., hemiplegia, paraplegia in extension) in which extensor reflex activity overshadows the flexor reactions, the so-called extensor plantar response is minimal, consisting mainly of the toe movements just described. The flexor nature of the reflex is shown, however, by the associated contraction of the ham-strings, i.e., semitendinosus, semimembranosus and biceps femoris, which invariably occurs (see also p. 870). Even when the toe movements do not

occur, some slight contraction of the ham-string can usually be detected. Its flexor nature is also indicated by the fact that an undoubted extensor reflex such as ankle clonus is readily inhibited by evoking the Babinski reaction (reciprocal inhibition). In hemiplegia in which the Babinski sign is present, stimulation of the sole of the *sou* side in some instances causes *plantar* flexion of the toes on the affected side together with contraction of the extensors of the knee and hip. This crossed response differs, however, from the normal plantar response (which of course is not crossed) in that contraction of the tensor fasciae femoris (a flexor does not occur. It is looked upon as a *true* extensor response corresponding to the crossed extensor reflex in the hind limb of the experimental animal when a flexion reflex is set up in the homolateral limb.



FIG. 370. Upper drawing, normal plantar response; lower drawing, Babinski response.

In the restricted forms of the extensor response as seen in hemiplegia, the receptive field of the reflex is also strictly circumscribed, being elicitable only from the sole—the outer border or the base of the hallux more especially.

In paraplegia in flexion in which flexor activity predominates the so-called extensor response is maximal and, as we have seen, is simply part of a widespread flexor reaction. The receptive field of the reflex is extensive and the application of stimulus is followed by contraction not only of the extensor longus hallucis and ham-strings but by an associated contraction of the extensor longus digitorum, tibialis anticus, gracilis, sartorius, rectus femoris and iliopsoas. The extensors undergo reciprocal inhibition. The flexor nature of the “extensor” response is therefore undoubted. It is a nociceptive reflex, the limb, when the reflex is fully developed, being withdrawn from the

⁴Holmes has denied that the evacuation of the bladder in response to peripheral stimulation is an integral part of the mass reflex, i.e., due to irradiation of impulses to the micturition center in the cord; he attributes it simply to the sudden rise in intraabdominal pressure caused by the associated reflex contraction of the abdominal muscles.

⁵An “extensor” plantar response is present normally in infants up to the first year or so, i.e., to the age of walking, and is then probably due to the undeveloped state of the corticospinal tracts. It is also present in normal adults during deep sleep (p. 917) and in the apneic stage of Cheyne-Stokes respiration, being apparently due in the latter instance, to anoxemia of the motor cortex.

stimulating (nocuous) agent by a flexion at hip and knee and dorsiflexion at the ankle.

OTHER REFLEXES

(a) *Oppenheim's reflex* is simply a modified Babinski response; it is associated with the same conditions as the latter and has a similar significance. It consists in dorsiflexion of the hallux which results when a firm downward sliding pressure is applied to the skin overlying the tibia.

(b) *Rossolimo's reflex* consists of flexion of the toes in response to a sharp tap upon the ball of the foot (see p. 890).

(c) *Nociceptive reflexes of upper limb.* A flexor reflex of the upper limb corresponding to the sign of Babinski of the lower limb is often elicitable in lesions involving the pyramidal tracts above the thoracic region, as in hemiplegia. It consists of flexion of the fingers, often accompanied by flexion of wrist and elbow and abduction and external rotation of the shoulder, when a mildly nocuous stimulus is applied to the palm or surfaces of the finger. Sometimes an extensor response—elevation, adduction and internal rotation of the shoulder, extension of the elbow, pronation of the forearm, flexion of wrist and hyperextension and adduction of the fingers—may be elicited in pyramidal tract lesion by stimulation of the skin of the axilla or side of the chest.

(d) *Abdominal reflexes.* Lightly scratching the skin of the abdomen of a normal person causes a reflex contraction of the abdominal muscles. The reflex is abolished in pyramidal lesions or in one (e.g., acute anterior poliomyelitis) involving the centers in the cord. The latter are located in the 7th to 12th thoracic segments.

(e) *Cremasteric reflex* consists of contraction of the cremaster muscle and elevation of testicle which results from a light stroke applied to the skin on the inner aspect of the upper part of the thigh. It is abolished in pyramidal lesions or as a result of destruction of the center which lies in the 1st lumbar segment.

(f) *Bulbocavernosus reflex* has its center in the 2nd, 3rd and 4th sacral segments. It consists of contraction of the bulbocavernosus muscle (detected by palpation) in response to stimulation of the glans penis.

(g) *Anal reflex* is the contraction of the external anal sphincter in response to scratching the neighboring skin. Its center is situated in the 4th and 5th sacral segments.

(h) *Gluteal reflex.* Scratching the skin of the buttock causes contraction of the gluteal muscles. It depends upon the integrity of the 4th and 5th lumbar segments.

The *deep or tendon reflexes*, such as the knee jerk, ankle jerk, etc., have been discussed in Chapter LXVI.

CHAPTER LXVIII

THE EXTRAPYRAMIDAL SYSTEM. THE THALAMUS AND HYPOTHALAMUS. THE VISUAL AND AUDITORY PATHWAYS.

There are at least two pathways other than the pyramidal or cortico-spinal through which the cerebral cortex exerts an influence upon the activity of the skeletal muscles, namely through the pons and cerebellum—the *corticopontocerebellar*—and through the striate body and the subthalamic nuclei—the *corticostrionigral*. The first mentioned of these two systems will be considered in chapter LXXI. The second will be considered here.

The corticostrionigral system embraces four masses of gray matter, (a) *the corpus striatum*, (b) *the red nucleus*, (c) *the substantia nigra* and (d) *the body of Luys*, which are referred to collectively as the basal ganglia. These several nuclear masses are connected together by numerous fiber tracts (fig. 371).

THE CORPUS STRIATUM

The corpus striatum is a mass of gray matter lying at the base of the hemisphere in close relation to the thalamus. It is incompletely divided into two parts by the fibers comprising the internal capsule: (a) the *caudate nucleus* lying on the medial side of the anterior limb of the internal capsule, and (b) the *lentiform nucleus* occupying a corresponding position on the outer side of the internal capsule (fig. 367, p. 863). The wedge-shaped lentiform nucleus is divided again into an outer and an inner part, the *putamen* and the *globus pallidus*, respectively. On the outer side of the lentiform nucleus is a narrow band of white matter—the *external capsule*; lateral to this again is an elongated island of gray matter—the *claustrum*.

The fiber system of the corpus striatum. The fiber connections may be divided into the following groups:

(1) *Fibers arising and ending within the corpus striatum (internuncial).* These pass from (a) the putamen to the globus pallidus (b) from the caudate nucleus across the internal capsule to the putamen and (c) from the lateral to the medial zone of the globus pallidus, (fig. 372).

(2) *Fibers arising in the corpus striatum and ending elsewhere (striofugal fibers).* The great bulk of the fibers leaving the corpus striatum arise from the globus

pallidus. (a) *Striothalamic* from globus pallidus to the lateral nucleus of the thalamus. Through these, and the thalamo-olivary and olivospinal tracts a possible pathway exists for striatal impulses to reach the spinal cord. (b) *Striosubthalamic (ansa lenticularis).* These arise in the globus pallidus and pass to the red nucleus, substantia nigra and the body of Luys. (c) There is no direct connection, apparently, between the corpus striatum and the spinal centers through, according to Morgan, a direct path (strio-bulbar) to the bulbar nuclei exists. These fibers arise in the globus pallidus. They terminate around cells in the reticular formation of the pons and medulla and in the trochlear, abducens, trigeminal (motor), glossopharyngeal and hypoglossal nuclei, of the same and the opposite side. The reticulospinal and rubrospinal tracts provide pathways whereby striatal impulses reach the spinal centers. No fibers passing from the striate body to the cortex were found by Wilson, who made a comprehensive study of the striatal connections. Others, however, state that such exist.

(3) *Fibers ending in the corpus striatum but arising elsewhere (striopetal fibers).* (a) *Thalamus to caudate nucleus and globus pallidus.* (b) *Body of Luys to globus pallidus.* (c) *Red nucleus to globus pallidus.* (d) *Cortex to caudate nucleus.* Area 6 (premotor) sends fibers to this part of the corpus striatum and possibly also to the globus pallidus (Hardesty).

(4) *Fibers joining the corpora striata of the two sides (commissural fibers).* These pass from the globus pallidus of one side to the corresponding nucleus of the opposite side.

(5) *Fibers passing through the corpus striatum (fibers of passage).* Ascending and descending fibers of internal capsule—corticospinal, thalamocortical, etc. (see fig. 367).

The corpus striatum is also almost certainly in communication with the cerebellum through relay stations, e.g., red nucleus.

THE RED NUCLEUS

The red nucleus is a large oval mass of gray matter in the tegmentum of the mid-brain lying beneath the thalamus and extending backwards from about the middle of this structure to a level beneath the posterior border of the superior colliculus (figs. 371 and 372). The fibers of the third nerve stream through it. Two groups of cells are found within it. The cells of one of these

groups are large (*nucleus magnocellularis*) and are situated at the posterior part of the red nucleus. The other, situated anteriorly, is composed of small cells (*nucleus parvocellularis*). Phylogenetically,

bar and rubrospinal tracts. The connections of the red nucleus are:

- A. Efferent tracts (rubrofugal).
 (a) Rubrobulbar and rubrospinal tracts from nucleus

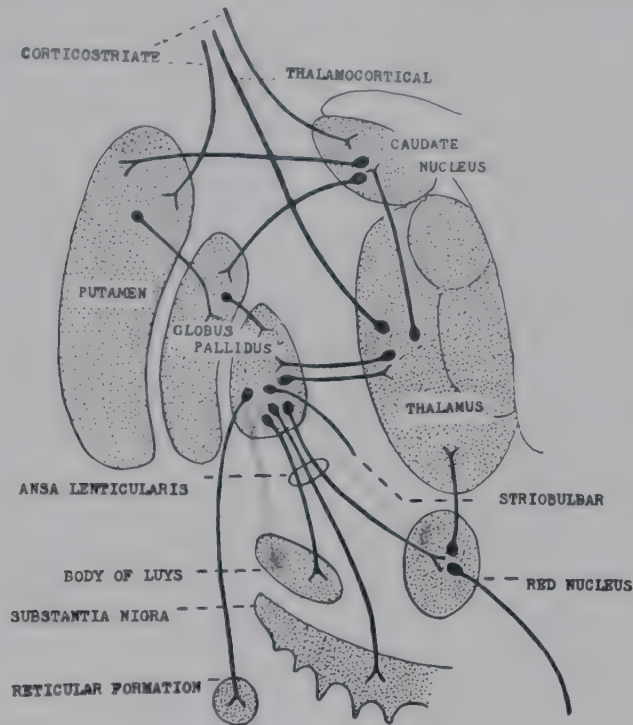


Fig. 371. Diagram of the corpus striatum and its connections.

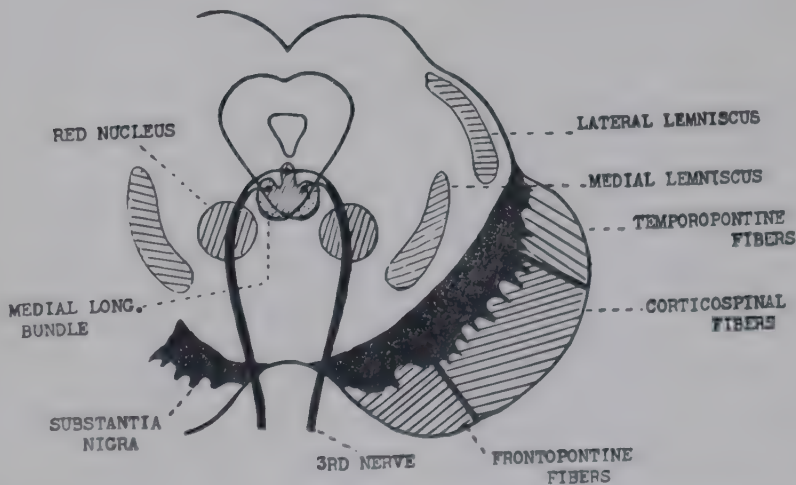


Fig. 372. Diagram of section through the mid-brain at the level of the red nucleus.

the nucleus parvocellularis is a later acquisition. Fibers arising from the nucleus magnocellularis of one side issue from the ventral aspect of the red nucleus and, crossing with those of the opposite side (Forel's decussation) descend as the rubrobul-

magnocellularis to the motor cells of medulla and cord (p. 856).

(b) To the reticular formation of the pons and medulla (tractus rubroreticularis).

(c) Rubro-olivary tract, to the inferior olivary nucleus.

(d) Rubrothalamic tract to the lateral nucleus of the thalamus.

(e) Rubrostriatal to globus pallidus.

B. Afferent tracts (rubropetal).

(a) Corticorubral tract, from the frontal lobe and premotor area to the nucleus parvocellularis.

(b) Pallidorubral tract from the globus pallidus.

(c) Cerebellorubral tract (p. 924) composed of fibers which arise mainly in the dentate nucleus of the opposite cerebellar hemisphere and reach the cells of the nucleus magnocellularis via the superior cerebellar peduncle. This cerebellar pathway is relayed to the bulbar and spinal centers by the rubrobulbar and rubrospinal tracts.

Little is known definitely with regard to the functions of the red nucleus. It appears, however, to be an essential part of the mechanism controlling the performance of complex muscular movements. It may be regarded as a center wherein impulses received from various sources (cerebral cortex, corpus striatum, cerebellum, etc.) are organized before their transmission (via rubrobulbar, rubrospinal and rubroreticular tracts) to the motor centers of the cranial and spinal nerves.

THE SUBSTANTIA NIGRA

The substantia nigra is the crescentic gray mass seen in transverse section lying ventral to the red nucleus and between the basal and tegmental portion of the cerebral peduncles (figs. 371 and 372). It is composed of large cells which are deeply pigmented with melanin and have a high content of iron. It is connected by both afferent and efferent fibers with the globus pallidus and the frontal region of the cerebral cortex. It also receives fibers from the body of Luys and from the medial and lateral lemnisci, the superior colliculus and the mammillary bodies. It is thus in receipt of afferent impulses from the general body surface and from the organs of hearing, sight and smell. It sends fibers to the red nucleus and to the formatio reticularis of the pons. The substantia nigra is regarded as a center for the integration of those afferent impulses which are essential for the performance of skilled movements. It shows its greatest development in man and the higher apes.

THE BODY OF LUYS OR SUBTHALAMIC NUCLEUS

The anterior limit of this structure lies on a level with the mammillary bodies. It should not be confused with the hypothalamic nuclei (p. 882). It lies lateral and ventral to the red nucleus and dorsal to the substantia nigra. Fibers

link it to both these structures and to its fellow of the opposite side. It receives fibers from, and sends a few fibers to the globus pallidus (p. 874).

THE EFFECTS OF EXPERIMENTAL STIMULATION AND INJURY OF THE BASAL GANGLIA

Phasic movements in any way like those which can be elicited by excitation of the motor cortex cannot be induced by stimulation of the basal ganglia or of the subthalamic region. When such movements occur they are attributed to the escape of current to the internal capsule. The slow movement of the legs of cats was observed by Miller upon unipolar faradization of the caudate nucleus or by the application of warm water or of strychnine, which appears to be due to the excitation of this nucleus itself. The outstanding result of stimulation of the striate body is observed during muscular movements initiated from the motor cortex or when the limbs are held by tonic postural contractions; then inhibition promptly occurs. Among the most definite experimental results are those of Mettler and his associates. They observed the following effects of electrical stimulation of the corpus striatum in monkeys. (a) Movements induced by excitation of the motor cortex were inhibited by concurrent stimulation of the caudate nucleus, putamen or claustrum; (b) stimulation of the globus pallidus added to movements initiated from the motor cortex, an element of "plastic tonus" which exerted a "holding" action upon the movements and prolonged their reaction time.

Experimental lesions of the striatal region in dogs or cats result in no noticeable motor defect and in monkeys is any pronounced effect observed. Kinnier Wilson found that when extensive unilateral lesions were made the animals used a preference for the arm and hand of the ipsilateral side and showed clumsiness of movement on the limb of the opposite side. There was, however, no paralysis or even paresis. In chimpanzees striatal injury is followed by athetoid movements (p. 878) closely similar to those seen in persons suffering from disease of this region. Brown observed tremors in monkeys following large bilateral lesions in the putamen or smaller bilateral lesions of the globus pallidus. Liddell and Phillips observed slight but persistent hypertonus in the extensor muscles of the opposite side and flexor hypertonus on the same side following electrolytic lesions in the corpus striatum. Placing reactions were imperfect and closure of the contralateral

eral eyelid was defective. The highest integrative level of the corticostriatonigral system consists of cells in areas 6 and 4 and especially in the strip of cortex (4; or "strip area of Hines") lying between these areas.

FUNCTIONS OF THE EXTRAPYRAMIDAL SYSTEM

The corpus striatum is one of the oldest parts of the cerebrum, and the globus pallidus (*paleostriatum*) is older phylogenetically than the putamencaudate portion (*neostriatum*). The connections of the paleostriatum are chiefly efferent; the neostriatum is mainly receptive. In lower vertebrates (e.g., fishes, amphibia, reptiles and birds), in which the cortical mantle is absent or rudimentary and the pyramidal system has not yet come into being, the corpus striatum¹ is the highest motor center, being looked upon as homologous with the motor cortex of higher forms. Upon this "old motor center" and its connections with lower levels very largely depend the motor activities of submammalian forms. In the bird, for instance, after removal of its rudimentary cortex, visual and auditory sensations seem unaffected and it continues to carry out normal movements of feeding, courting, fighting, etc. These instinctive reactions are imperfectly executed after removal of portions of the striate body. With the evolution of the cortex and the arrival of the pyramidal tracts (in mammals) the functions of the extrapyramidal system though subordinated to those of the motor cortex are not lost but, on the contrary, carry out those more or less automatic or reflex movements concerned with the maintenance of posture, defence, feeding, etc. In the cat or dog for example almost normal activities can be executed after destruction of the pyramidal system (by removal of the cortex). The extrapyramidal paths undoubtedly play an important rôle in the ordinary motor activities of these animals. In man the cortical representation of the extrapyramidal system is probably in the premotor area (p. 888). Wilson's view of the functions of this system in the human subject is that through the convergence of its paths upon the spinal motor neurons it maintains a postural background against which voluntary movements are executed. Impulses traveling these paths exert, he believes, a steadying

effect upon, but do not themselves initiate, such movements. Kappers, however, considers that the habitual or automatic acts of daily life are mediated through this extrapyramidal system and points out that such types of movement suffer the greatest impairment in striatal disease.

CLINICAL MANIFESTATIONS OF DISEASE OF THE EXTRAPYRAMIDAL SYSTEM

The chief clinical features of extrapyramidal disease are: (a) muscular rigidity resulting in disturbances of posture and movement, (b) involuntary movements, e.g., tremor, athetosis, chorea. (c) absence of any true paralysis. The corpus striatum and other parts of the extrapyramidal system seem to be peculiarly susceptible to the actions of certain toxic substances. The following are some of the syndromes met with: (1) *Progressive hepato-lenticular degeneration*, (2) *Parkinsonism*—paralysis agitans, etc., (3) *chorea*, (4) *athetosis*, (5) *tortion spasm*.

HEPATO-LENTICULAR DEGENERATION (WILSON'S DISEASE)

This was described by Wilson in 1912. It invariably terminates fatally but its duration varies from a few months to several years. The following are its chief features:

(a) *Muscular rigidity* is wide spread and progressive; it involves face, trunk and limbs. Flexors as well as extensors are affected, but the former more conspicuously than the latter. The hypertonus offers a "lead-pipe-like" resistance to passive movement and results in slowness and difficulty of movement. Eventually, the patient is rendered almost immobile as though carved from stone; he can be lifted or moved *en bloc*. The rigidity of the facial muscles gives a fixed, immobile expression. The mouth is sometimes held widely open; the smile or laugh is peculiarly stiff and vacuous. The hypertonus of the muscles of articulation and deglutition leads to dysarthria (p. 899) and dysphagia. The rigidity is temporarily abolished by the injection of novocaine into the muscles and therefore dependent upon afferent impulses.

(b) *Involuntary movements*. These consist chiefly of tremor (about 6 oscillations per sec.) which is increased by excitement or any attempt at voluntary movement; sometimes athetoid movements (p. 878) occur.

(c) *The reflexes are normal*. There are no sensory changes and although the muscles often show some weakness and are easily fatigued there is no actual paralysis.

(d) *Cirrhosis (multilobular) of the liver* is found at autopsy, but during life there may be no signs of liver disease. In some instances, however, symptoms pointing to the liver precede the nervous manifestations.

¹ The infant's movements are of such a nature as to suggest that they are under the control of the extrapyramidal system, the pyramidal system being as yet not fully developed.

(e) *Emotionalism*. Involuntary laughing or crying, and some mental deterioration.

(f) *Greenish brown pigmentation of the cornea (in Descemet's membrane) occurs in a proportion of cases.*

Degeneration of the cells of the putamen and sometimes cavity formation are found at autopsy. The caudate nucleus and globus pallidus are affected to a much less degree. A toxin of some sort is probably responsible for the disease. It is possible that the toxic substance is absorbed from the alimentary canal, and damages both hepatic and nervous tissue.

THE PARKINSONIAN SYNDROME

The principle features of this syndrome are the following: (a) A *coarse tremor* involving head and limbs. The hand may show pill-rolling movements, i.e., rhythmical movements of thumb upon the first two fingers; alternating movements of flexion and extension at the wrist, or of supination and pronation of the forearm, are frequently present. When the limb is engaged in some voluntary act the movements often temporarily disappear in that limb but become more pronounced in other parts. (b) *Muscular rigidity* which leads to slowness and stiffness of movement and a fixed mask-like expression (Parkinson's mask); the patient winks infrequently, and speech is slow. The upper limbs are held in characteristic attitudes of adduction at the shoulders, flexion at the elbows, flexion or slight extension at the wrists, flexion at the metacarpophalangeal joints and slight flexion at the interphalangeal joints. (c) The *gait* is slow and shuffling with short steps, or it may be "festinating" in character, i.e., the patient is bent forward and hastens along with short quick steps as though trying to "catch up to his center of gravity" and prevent his falling. When pushed forward or backward he cannot stop quickly but moves by a series of small rapidly repeated steps in the direction in which he is pushed. *Propulsion* and *retropulsion* are the respective terms applied to these forward and backward movements. There is no true paralysis; the reflexes and sensation are unaffected. The condition is due to degenerative changes in the corpus striatum; according to Hunt, the chief lesion is a progressive atrophy of the globus pallidus. Degeneration of the muscle spindles also occurs.

The picture of Parkinsonism just drawn is one which is seen in elderly persons; it occurs without apparent cause and is slowly progressive. It is also spoken of as *paralysis agitans*. Other forms of Parkinsonism, essentially the same in their manifestations but differing in detail may

occur at any age and develop more rapidly as result of *epidemic encephalitis* (encephalitis lethargica). Rigidity is the most prominent feature of the post-encephalitic type—choreic and athetoid movements may also occur. The patient may assume statuesque attitudes for long periods—*catatonia*—or maintain the limb in a position which has been passively imposed upon it. The substantia nigra is particularly chosen for attack in this type. The locus coeruleus in the floor of the 4th ventricle is also affected in a proportion of cases, and this fact may account for the disturbances in the autonomic nervous system which is sometimes a prominent feature (McAlpine). Trauma and poisoning by carbon monoxide or manganese are unusual causes of Parkinsonism. It may also result from cerebral arteriosclerosis.

ATHETOSIS (MOBILE SPASM)

This is the term applied to movements of a peculiar slow writhing, twisting or squirming character involving the upper limbs and less commonly the face and lower limbs. They may be unilateral or bilateral. They are increased when any voluntary movement is attempted but disappear during sleep. The muscles when not actually engaged in the abnormal movement are hypotonic. As seen in the hand the movement consists of alternate extension and flexion at the wrist and metacarpophalangeal joints, with the fingers usually held extended at the interphalangeal articulations. Involvement of the facial muscles results in grotesque facial expressions (grimacing); involvement of the muscles of the mouth and throat causes disturbances of articulation and of deglutition.

Though athetoid movements occur in lesions of the pyramidal paths the presence of some intact pyramidal fibers has been considered to be essential for their occurrence; the movements are abolished if as a result of subsequent lesion the pyramidal pathway is completely interrupted. For example, extirpation of, or the injection of alcohol into, the motor area of the cortex governing the muscles involved prevents the movements. Wilson believes that the abnormality is due to degeneration of the cerebello-rubrothalamo-cortical pathway and the release of the pyramidal system from a controlling influence. The following observation suggests, however, that the impulses giving rise to the movements travel over extrapyramidal paths (from motor area via the striate body to spinal centers).

(a) Division of the anterior columns of the cord (which, through the reticulospinal tracts, are believed to transmit striatal impulses) in a subject of athetosis abolished all abnormal movements below the section level, but left voluntary (pyramidal) innervation unimpaired.

(b) Bucy and Buchanan have reported the case

a child whose athetoid movements were abolished permanently by the excision of the central part of the precentral gyrus (i.e., area 6a α of the premotor cortex, p. 888) leaving the motor area almost intact. These observers suggest that the movements are due to a hyperexcitable state of area 6a α , and that their cessation, following injury to the pyramidal tracts, is in reality due to the interruption of the connections of this area with the motor cortex (area 4).

(c) Lesions in the striate body, substantia nigra or body of Luys have been found at autopsy in cases which had shown athetosis. It also occurs in conditions such as cerebral diplegia, in which the premotor as well as the motor area is frequently injured.

CHOREA

There are two principal forms of this condition.

(1) **SYDENHAM'S CHOREA** (or St. Vitus's dance) is not uncommonly a sequel to acute rheumatism. Its chief features are: (a) involuntary jerky movements, semi-purposeful in character, involving the muscles of the limbs and face. They are intensified by excitement but disappear during sleep. The mobility of the face is in marked contrast to the fixed "starched" expression of Parkinsonism. There may be athetoid movements, the condition then being termed *atheto-chorea*. (b) Hypotonia of the muscles.

Sydenham's chorea may be bilateral or unilateral (hemichorea). Death is rare and there is consequently uncertainty concerning its neuropathology. The lesions are probably similar in nature to those responsible for athetosis. Degenerative changes in the corpus striatum (chiefly in the putamen and caudate nucleus), substantia nigra and body of Luys have been described in fatal cases. Hemorrhage into the body of Luys of one side has been found in hemichorea.

(2) **HUNTINGTON'S CHOREA** is a much more serious affection, being usually fatal. It is hereditary, showing Mendelian dominance. Of about 1000 cases arising in the United States practically all can be traced to some half dozen individuals, including three brothers who settled there in the 17th century. The choreiform movements are often violent; there are dysarthria, ataxia of the limbs and progressive dementia. The changes in the central nervous system are, marked atrophy of the cerebral cortex and the corpus striatum. Of the latter, the putamen and caudate nucleus are involved; the globus pallidus escapes.

Tortion spasm is a very rare condition and need only be defined. It consists of spasms of neck, trunk and limb muscles which twist the body into bizarre attitudes. The muscles, following the spasm, are hypotonic. Pathological changes in various parts of the extrapyramidal system have been described.

THE THALAMUS

This large gray mass is related medially to the 3rd ventricle which lies between the thalami of the two

sides. The posterior limb of the internal capsule lies upon the outer side of the thalamus and separates it from the lentiform nucleus. Above the thalamus is the lateral ventricle, a part of whose floor it forms. In front is the head of the caudate nucleus; the arched body of the latter is related to the upper part of the lateral surface of the thalamus. Below the thalamus are the red nucleus, corpus of Luys and substantia nigra (subthalamic region). (Fig. 371.)

The thalamus contains five main nuclear groups, 1, *anterior*, 2, *ventral*, 3, *dorsomedial*, 4, *lateral* and 5, *nuclei of the mid-line*. The *anterior nuclei* form a mass which bulges into the lateral ventricle and consists of three distinct groups of cells, the *anterodorsal*, *anteroventral* and *anteromedial* nuclei. The anterior nuclei receive fibers from the mammillary bodies (mamillo-thalamic tract of Vicq d'Azyr) which convey olfactory impulses. They send fibers to the paracentral lobule and the cingular gyrus on the mesial aspect of hemisphere.

The *ventral nuclei* consist of two cell groups, the *lateroventral* and the *posteroventral* nuclei. The lateroventral nucleus receives fibers from the dentate nucleus of the cerebellum via the brachium conjunctiva and sends fibers to areas 4 and 6 of the cerebral cortex, the forepart of the nucleus being connected with the foot area of the cortex, the central part with the arm area, and the medial portion with the cortical area governing the facial muscles. The posteroventral nucleus is the main relay station for afferent impulses travelling to the cerebral cortex. It receives fibers from the spinothalamic tract, from the nuclei of the posterior columns and from the trigeminal nuclei. It sends fibers to the postcentral convolution.

The *dorsomedial nucleus*. This, like the lateral nucleus, is an association center. It is connected by many fibers with the lateral nucleus, and with the hypothalamus and the prefrontal area of the cerebral cortex.

The *lateral nucleus* consists of a *dorsal* and a *posterior* portion. The main connections of the dorsal part are with the ventral group of nuclei. The posterior part receives fibers from the dorsal region and from the tectum. Fibers connect it with the parietal cortex exclusive of the postcentral gyrus. The expansion of the posterior part of the lateral nucleus which overhangs the superior colliculus is known as the *pulvinar*. Cells in the inferior part of the nucleus send fibers to the cortex adjacent to the visual area (area 18) while the main part projects to the cortex adjacent to the auditory area.

Mid-line nuclei. These nuclei are situated in that part of the thalamus which forms the upper part of the wall of the third ventricle. They are connected by many fine myelinated fibers with subcortical centers, namely, the hypothalamus and mid-brain nuclei. They also receive fibers from the corpus striatum. These nuclei have many intrathalamic connections but few if any fibers connect them with the cerebral cortex.

It will be seen from the foregoing account that the nuclei of the thalamus can be divided upon a functional basis into three categories, namely, (a) those which serve as relay stations of afferent impulses from the periphery to the cortex, (b) those which are connected mainly with subcortical centers and (c) those whose chief function is associative.

The thalamus (which portion is undecided) also sends fibers to the olivary nucleus (*thalamo-olivary tract*).

Functions

We have seen that the corpus striatum represents the highest level of an old motor system. The thalamus, on the other hand, is a primitive receptive center wherein sensory impulses give rise to a *crude uncritical form of consciousness*. It serves as a great integrating center; through its connections with the corpus striatum, tactile, painful, olfactory and gustatory impulses are correlated with motor reactions. Sensory localization in the thalamus has been demonstrated by Dusser de Barenne and Sager by means of local strychninization. The injection of a minute quantity of the drug into the thalamus in cats is followed by hyperesthesia and hyperalgesia to cutaneous and deep (muscle, tendon and periosteum) stimuli. The cutaneous hypersensitivity is most pronounced on the contralateral side of the body; increased sensitivity to deep stimuli occurs only on the contralateral side. By this method, *sensory areas in the lateral nucleus* of the thalamus for the head, arm and leg have been located. These areas are not, however, sharply delineated as in the cerebral cortex but show rather wide overlapping.

The thalamus is not, however, entirely sensory in function. In animals possessed of little or no cortex, or in higher mammals (e.g., cat or dog) after decortication, it and the corpus striatum serve for the execution of complex movements of an automatic or reflex nature. Motor responses also result from its direction stimulation. Conjugate deviation of the head and eyes to the opposite side and movements of progression in the limbs follow electrical excitation of the ventral nucleus. The pulvinar has in the past been looked upon as a relay station in the transmission of visual impulses to the occipital cortex. It now appears, however, from the researches of Brouwer and Zeeman that though this part of the thalamus receives fibers of the optic tract, it is not a primary visual center (see p. 1008).

The regrouping of afferent impulses within the thalamus

The clinical researches of Head and Holmes indicate that the various types of sensory impulse which reach the lateral nucleus are regrouped. The cruder, more essentially primitive sensation (protopathic), e.g., *pain, extremes of temperature, pressure, and contact* over hair-clad parts are relayed to and terminate in what has been called by Head and Holmes "the essential organ of the thalamus." This probably corresponds to the medial nucleus. Impulses arriving in the "essential organ" arouse a type of consciousness or "crude awareness" in which the character of the sensations comes under the category of "feelings (affective sensations), both pleasurable and disagreeable. They are devoid of discriminative qualities. Fibers subserving the finer discriminative sensations are relayed from the lateral nucleus of the thalamus to the somaesthetic area of the cortex (fig. 373). These latter fibers ascend through the posterior limb of the internal capsule (thalamic radiation) and apparently are in five groups, mediating respectively the following sensations:

- (a) Light touch to hairless parts.
- (b) Localization of the point touched.
- (c) Spatial discrimination.
- (d) Temperatures between 25° and 40°.
- (e) Position and passive movements of the limbs.

Thalamic lesions

The effects resulting from a lesion involving the lateral thalamic nucleus will resemble those following an interruption of ascending pathways in the brain stem above their decussation. That is, all types of sensation on the opposite side of the body tend to be lost or grossly affected, or there may be severe pain as a result of destruction of inhibitory mechanisms or possibly of the direct stimulation (irritation) of pain fibers. A lesion involving the fibers after regrouping (i.e., after the epicritic types of sensation have been sorted from the cruder sensations and are ascending to the cortex) will cause a loss of the discriminative types of sensation alone. A lesion in the internal capsule (thalamic radiation) or corona radiata might have such an effect (see pp. 862, 863).

THE THALAMIC SYNDROME ("SYNDROME THALAMIQUE") OF DÉJERINE AND ROUSSY. This is

characteristic picture occasionally seen in thalamic disease. The following are its chief features:

(1) Astereognosis and slight ataxia, due to the loss of the sense of position. These and the other effects given below are of course on the side of the body opposite to that of the lesion.

(2) Some loss of tactile and thermal sensations over the body and face. The threshold for pain is frequently raised. The loss of sensation is variable both in degree and type, depending upon

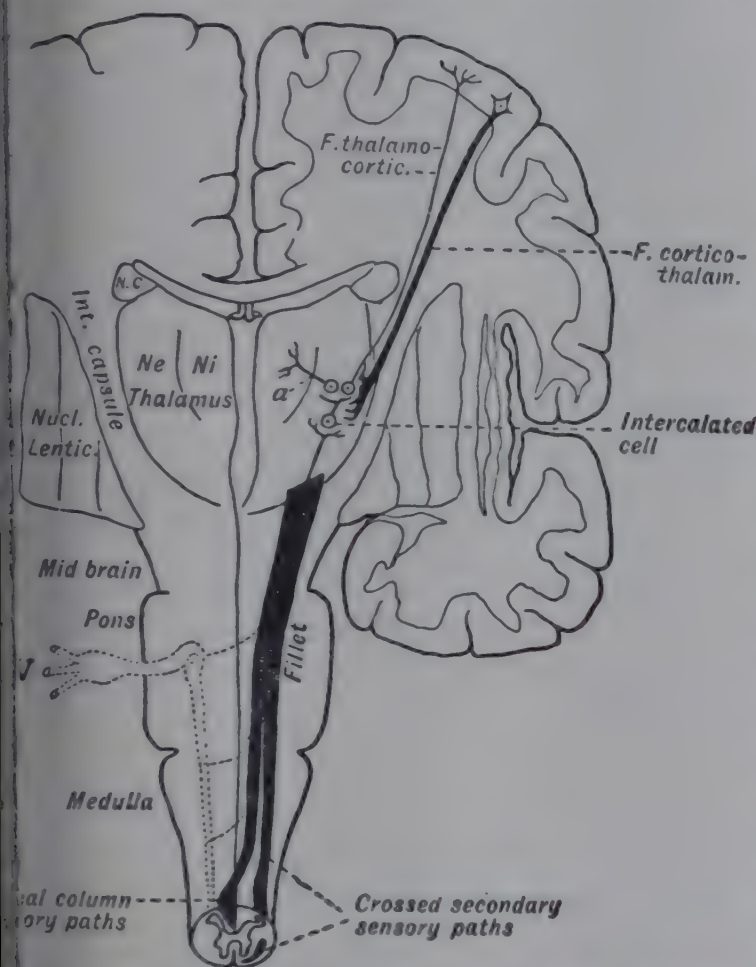


FIG. 373. Diagram showing the paths and centers concerned in sensation. All sensory impulses ascend to the lateral part of the thalamus, where regrouping occurs; the cruder sensations (e.g., those of pain and extremes of temperature) are relayed to the medial portion of the thalamus, the remainder (e.g., light touch, discrimination of two points, sense of position and movement, etc.) to the cerebral cortex. The corticothalamic fibers, which terminate in the lateral nucleus of the thalamus are also shown (after Head).

the extent of the lesion. In some instances the sensory loss is slight.

(3) Spontaneous pain occurring in paroxysms and often excruciating in character. The pain may be so intense as to resist the action of powerful sedatives, e.g., morphine. A painful stimulus is felt much more acutely than is normal (hyperaesthesia); and though, as mentioned above, the threshold for pain is often raised, the sensation when once aroused (by increasing the strength

of stimulus) is excessively severe. The spontaneous pain and the magnification of the response to painful stimuli are usually referred to as the *thalamic over-reaction*.

The over-reaction phenomena are due, according to Head and Holmes, to the release of the "essential organ of the thalamus" from the restraining influence which the cortex exerts normally through the corticothalamic fibers. The symptoms are the result of a lesion involving these fibers or their connections in the lateral part of the lateral nucleus of the thalamus.³ But the sensory disturbances just described are not associated exclusively with thalamic lesions; they may also be caused by disease of the brainstem, spinal cord or even of the peripheral nerves. Kendall has offered an explanation for the disturbances of sensation, especially of the over-reaction on the basis of the existence of two central pathways for pain—a rapidly conducting and a slowly conducting system of fibers, the former exerting an inhibitory influence upon the latter. Interruption of the fibers of rapid conduction, which are thought to transmit the epicritic sensations, would account for the blunting of tactile and thermal perception and would allow a greater response of the slowly conducting system over which, it is suggested, protopathic sensations are transmitted. Kendall draws attention to a familiar experience, namely, the more intensely painful sensation which follows a little time after the immediate response to a painful stimulus. The delayed sensation, which is most commonly felt when the skin comes into contact with a very hot object, appears to be similar in quality to that described as being characteristic of the thalamic syndrome (see p. 802). The thalamic syndrome includes other unpleasant sensations; even a form of stimulation, such as tickling the sole of the foot, which produces no discomfort on the sound side, is highly unpleasant on the other side. Many patients complain that shaving the affected side of the face feels as if the razor were being drawn over a raw surface. Even cutting the hair or nails may be objected to as being extremely disagreeable.

Sensations of pleasure are also increased in intensity. Warmth applied to the skin may cause the keenest en-

³ The persistence of a long period of the phenomena of over-reaction together with the exaggerated sensations of pleasure argue against their being simply due to the irritation of sensory paths. It is also doubtful whether the pain is truly spontaneous; it is more probably the result of some mild but undetermined stimulus

joyment and evoke such expressions as "exquisite," "lovely," etc. The patient, however, may be quite unable to appreciate that the sensation is one of warmth. During emotion disagreeable sensations occur on the affected side. Thus one of Head's patients was so affected by music that "he could not stand the hymns on his affected side," another said that when the choir sang "a horrid feeling came on the affected side and the leg . . . started to shake." In another patient pleasant feelings of a psychic nature were referred to the abnormal side. He said "I seem to crave for sympathy on my right side," and "My right hand seems to be more artistic."

THE HYPOTHALAMUS

The hypothalamus is the basal part of the diencephalon (interbrain). It lies in relation to

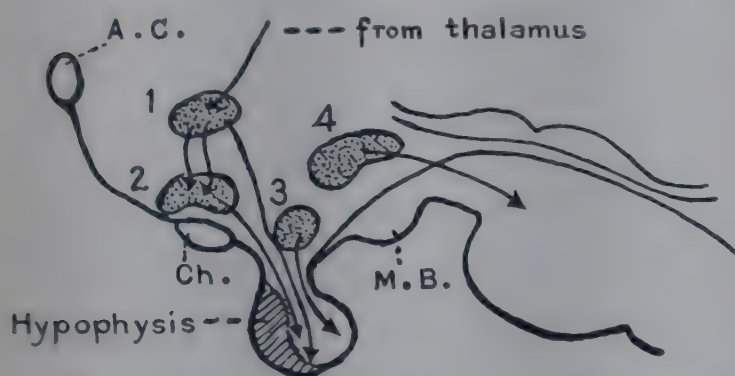


FIG. 374. The hypothalamic nuclei and connections. A.C., anterior commissure; Ch., optic chiasma; M.B., mammillary bodies. Nuclei; 1, paraventricular; 2, supraoptic; 3, tuber cinereum; 4, posterior hypothalamic.

the floor and lower parts of the walls of the 3rd ventricle (fig. 374). From a strictly anatomical point of view it may be taken to include the following structures: (a) *optic chiasma*, (b) *tuber cinereum* and the other nuclear masses in relation to the floor and ventral parts of the walls of the 3rd ventricle, (c) the *pituitary gland*, (d) the *corpora mammillaria* and (e) the *subthalamus* (p. 876). In physiological literature the term has usually a more restricted connotation including only (b) and (d) (see also p. 722).

Of the *nuclei of the hypothalamus* the greatest interest from the physiological point of view centers around the following.

The *supraoptic nucleus* lies above the optic chiasma and the commencement of the optic tract of the corresponding side. The *paraventricular nucleus* is situated above the supraoptic nucleus and is in close relationship medially to the wall of the 3rd ventricle and laterally to the column of the fornix. The *posterior hypothalamic nucleus* lies in the posterior part of the hypothalamus in relation to the wall of the 3rd ventricle; it extends backwards over the mammillary region. The *tuber cinereum* is a small eminence of gray matter

situated at the base of the brain between the optic chiasma and the mammillary bodies, i.e., in the posterior region of the hypothalamus. Out of it grows the pituitary stalk. Two groups of cells can be clearly defined within it; they are known as the *dorsomedial* and *ventromedial hypothalamic nuclei*.

Fiber connections. The hypothalamus receives fibers from the thalamus, and through the *medial forebrain bundle*, from the olfactory lobe and the parolfactory area. The medial forebrain bundle sweeps through the hypothalamus and in its course gives off fibers to several of the hypothalamic nuclei. It has been suggested on the basis of physiological experiments that a direct connection exists between the cortex and the hypothalamus, but such has not been demonstrated histologically. There seems little doubt, however, that a part of the brain is in communication with the cerebral cortex through indirect paths, e.g., through the thalamus. Efferent tracts descend from the hypothalamus through the midbrain and probably to the spinal cord. The various hypothalamic nuclei are in communication with one another through fiber tracts; the best known of these is the paraventricular-supraoptic tract, but others undoubtedly exist.

The supraoptic, paraventricular and tuberal nuclei are linked with the hypophysis by efferent fibers which descend the infundibular stalk (hypothalamo-hypophyseal tract). The majority of these fibers terminate around the pituicytes of the pars nervosa but some can be traced into the pars intermedia and the pars anterior (p. 1214).

THE PHYSIOLOGY OF THE HYPOTHALAMIC NUCLEI

Recent experimental and clinical investigations have revealed the hypothalamus as a region of great physiological importance. Our knowledge of the functions of this part of the cerebrum is still, nevertheless, very incomplete. Much of the evidence is suggestive rather than conclusive and permits only tentative views to be held concerning many of its activities. It is the general opinion, however, that in this part of the diencephalon are contained the mechanisms for the control of certain primitive reactions (visceral and somatic) associated in animals with defence, attack, and in man with emotional states (fear, anger, etc.). This region is also believed to contain centers for the regulation of certain fundamental and vital processes, e.g., fat, carbohydrate and water metabolism, and to exert a governing influence upon the body temperature, the gas movements, the genital functions and the sleep rhythm (p. 918).

It is now generally conceded that important centers governing the activities of the autonomic nervous system are situated in the hypothalamus.

Those cell groups in the anterior part of the hypothalamus and in the tuberal region are believed to constitute a parasympathetic center, whereas from the posterior part a directing influence is exerted over sympathetic functions.

The pituitary and the nervous structures of the hypothalamus are intimately associated in function; indeed, they should be considered together as constituting a closely integrated neuro-glandular mechanism rather than as possessing distinct and independent functions. It will be recalled that the pars nervosa of the pituitary is developed as a downgrowth from the floor of the 3rd ventricle, and that the pituicytes are modified neuroglial cells. On the other hand, the cells of the supraoptic and paraventricular nuclei of the hypothalamus show evidence of secretory activity. They have not the appearance of typical nerve cells for they contain granules resembling those found in glandular cells and droplets or larger collections of a colloid material can be observed within their cytoplasm; they also show vacuole formation which is rarely encountered in nerve cells. The rich vascular network which surrounds the cells of these nuclei, capillaries in some instances actually penetrating their protoplasm, strongly suggests a glandular function.

A brief summary of the experimental evidence relating to hypothalamic functions will be given in the following paragraphs.

(1) Karplus and Kreidl were the first to furnish evidence of a sympathetic center in the hypothalamus. Upon electrical stimulation of this region they obtained pupillary dilatation, sweating and a rise in blood pressure. Inhibition of intestinal movements also results. Liberation of adrenaline has also been reported to follow stimulation of the hypothalamus. By means of needle electrodes inserted into the region of the lateral nucleus Bronk and his colleagues have recorded impulses from sympathetic efferent nerves during stimulation of the hypothalamus. On the other hand, rhythmical variations in potential were produced in the hypothalamus by the stimulation of certain afferent nerves through which reflex sympathetic responses may be elicited.

(2) Beattie, Brow and Long found that extrasystoles produced in the cat by means of chloroform anesthesia, and which had been shown by Levy to be dependent upon sympathetic impulses (p. 198), were abolished by a destructive lesion placed in the posterior hypothalamic nuclei or by section of the brain behind this region. Stimulation of the posterior hypothalamic region, on

the other hand, caused extrasystoles to appear in an animal which previously had been free from these cardiac irregularities. Animals subjected to such lesions also showed hyperglycemia and glycosuria. Drowsiness for two or three days following the operation was a noticeable feature in some animals; they also showed a change in behavior, being more docile and "tamer" after the operation (see "sham rage" below). The nervous system of animals examined histologically some time after the lesions in the posterior hypothalamic nuclei had been made showed degenerating fibers which entered the mid-brain and descended through the brain stem and cord. Those in the latter situation entered the lateral column of gray matter at different levels down to the 3rd or 4th lumbar segment.

(3) Decerebration by a section through the mid-brain causes a profound fall in body temperature. No such loss of temperature control follows the removal of the cerebral cortex and thalamus, provided that the hypothalamus is left intact. It is significant that sympathetic effects, e.g., adrenaline liberation, ruffling of feathers or hairs, constriction of vessels and goose flesh, result from exposure to cold. Moreover, Cushing calls attention to the high temperature which frequently follows operations upon tumors in the region of the 3rd ventricle (see also p. 630).

(4) Hess fixed electrodes in the hypothalamus of cats. After the animals had recovered from the operation, a weak electric current passed through the hypothalamus induced a state indistinguishable from normal sleep. He also states that ergotoxin injected directly into the hypothalamic region induces sleep. This observation is, however, difficult to reconcile with the fact mentioned below that the intravenous injection of ergotoxin produces sham rage. Sham rage and other manifestations characteristic of hypothalamic stimulation also follow the local injection of a minute amount of strychnine.

(5) Kabat and associates by means of an electrode fixed in the hypothalamus stimulated this region in the unanesthetized animal. Pupillary dilatation, erection of hair, inhibition of gastrointestinal peristalsis, clawing and urination resulted. Stimulation of other parts of the brain produced none of these effects.

(6) The production of gastric lesions by hypothalamic injury and of ovulation by stimulation of the hypothalamus or of the hypothalamo-hypophyseal nerve tracts have been mentioned (pp. 446 and 756). Evidence for the control of

gastric motility by the hypothalamus has been cited on page 489.

Quasi-emotional state—"sham rage"

It was first demonstrated by Goltz that the reactions which usually accompany displeasure and anger are more readily evoked in an animal deprived of its cerebral cortex (decorticated) than in the normal animal. In Goltz's classical experiment the hemispheres and a large part of the thalamus were removed from a dog. The disposition of the animal was greatly altered by the operation, it being very readily aroused to anger. Barking, growling, baring the teeth or snapping occurred upon the least provocation. Cannon and Britton produced a similar state in cats by removal of the cortex, the decortication being performed by means of a pointed stilet inserted through the orbital cavities. Immediately following recovery from the anesthetic the animals showed the following remarkable phenomena which these observers termed "sham rage";—lashing of the tail, erection of the hairs, protrusion of the claws, dilatation of the pupils, sweating, struggling and biting, greatly increased rate of respiration and a rise in blood pressure. Most of these manifestations will be recognized as being of sympathetic origin. In many instances the picture is a combination of fear and anger. Liberation of adrenaline, as indicated by an increase in the rate of the denervated heart (p. 690), also occurred. The mildest stimulus such as jarring the table or lightly touching the animal was sufficient to evoke a paroxysm of rage. In his decortication experiments Bard found that the posterior and ventral portion of the diencephalon was essentially responsible for the development of "sham rage." The typical quasi-emotional behavior occurred after decortication and section through the hypothalamus at about the middle of the tuber cinereum. It also resulted from an operation which removed the corpora striata and the dorsal half of the diencephalon, i.e., the thalamus, but left the hypothalamus connected with the mid-brain. The condition failed to appear if the section separated the caudal part of the hypothalamus, i.e., the portion containing the posterior group of hypothalamic nuclei (p. 882), from the mid-brain. Taking the results of decortication experiments as a whole, one is led to the conclusion that the activities of the hypothalamus are normally under inhibitory influences from the cerebral cortex and that "sham rage" is the result of the release of these primitive subcortical centers from

higher control. Fulton and Ingraham, for instance, found that in order for the typical behavior to ensue decortication is unnecessary. Bilateral incision of the medial surface of the cerebral hemisphere in front of the optic chiasma is sufficient to produce hypothalamic over-reaction. Typical "sham rage" can be produced in intact cats by the intravenous injection of ergotoxin. It has been suggested that certain conditions in man, e.g., the manifestations of fear in shell-shock, the unreasoning rage of drunkenness, and the emotional instability of certain mental derangements associated with degenerative changes in the cortex may be due to the release of the hypothalamus from cortical control.

The evidence provided by the observations of Cushing and of Penfield for the existence of a parasympathetic center in the hypothalamus (p. 735) and the influence of this part of the brain upon water (p. 739), fat (p. 741) and carbohydrate metabolism (p. 593) are considered elsewhere.

DISORDERS OF THE HYPOTHALAMUS

The effects which may result from lesion (e.g., tumors, encephalitis, etc.) involving the hypothalamic region fall into the following groups: (a) disturbances in fat, carbohydrate or water metabolism (p. 739), (b) disorders of sleep, drowsiness, somnolence and, less commonly abnormal wakefulness, or reversal of the sleep rhythm,³ (c) emotional manifestations, laughing, crying, or a state resembling "sham rage" in animals, may result, (d) phenomena attributable to sympathetic or parasympathetic stimulation (e) disorders of the sexual functions.

Any one of the foregoing groups of effects may dominate the clinical condition to give rise to one or other of the following syndromes:

- (a) Diabetes insipidus.
- (b) Dystrophia adiposo-genitalis.
- (c) Laurence-Biedl-Moon syndrome.
- (d) Autonomic diencephalic epilepsy.
- (e) Narcolepsy.

These several conditions, with the exception of the last (e), have already been considered in the chapter devoted to the pituitary gland.

Narcolepsy (see also p. 918)

This is the term applied to a disturbance in the sleep mechanism in which sudden attacks of an irresistible desire for sleep occur during the day-time. The dura-

³ See Fulton and Bremer.

tion of the attacks, which resemble normal sleep, is quite brief—from a few seconds to 20 minutes or so. It is only to such sudden and brief naps, and not to persistent drowsiness or to prolonged periods of pathological sleep that the term is applicable. Nocturnal sleep may be normal but it is often disturbed or there may be insomnia. Sleep may overcome the subject of narcolepsy while he is going about his usual occupation, while walking, in the middle of a conversation, during a meal, driving a car, etc. There may be many attacks during the day. A few cases were discovered during the war in soldiers under trial by court-martial for falling asleep on sentry duty. The condition may be a sequel to influenza or to epidemic encephalitis involving the hypothalamus or may result from a tumor in this region. In other instances the condition follows a head injury or appears without known cause (idiopathic narcolepsy). Though evidence is not conclusive, it is very likely that in these latter, also, disordered hypothalamic function is responsible, for other features, e.g., obesity, polyuria or impairment of the sexual functions, pointing to an abnormality of this region are frequently present. *Ephedrine sulphate* (25 mgm. three times daily) or *benzedrine* is used with benefit in idiopathic narcolepsy. *Cataplexy*⁴ is the term given to a condition allied to, and very frequently associated with narcolepsy, in which the patient as a result of some emotion—amusement, anger, fear, embarrassment or surprise—is seized with complete helplessness. The attack

is brief, lasting for a few seconds, or for a minute or two at the most. Consciousness is not lost but the muscles are completely toneless and powerless for the time, and if the subject is attacked while standing his knees fail him and he sinks to the ground. The deep reflexes are lost. A normal person may become "weak with laughter," be "struck all of a heap," or "transfixed" when surprised or shocked. Or his jaw may "drop" when confronted with some unexpected occurrence. Cataplexy is regarded as an exaggeration of this normal tendency, just as narcolepsy is an intensification of the desire of many normal persons to drop into a doze under certain circumstances. Mirth is especially likely to precipitate a cataplectic attack. One victim reported by Adie remarked, "at the scout's camp the boys used to amuse themselves by making me laugh and then running away leaving me helpless on the ground." Even amusement without laughter will induce the helpless state in a susceptible subject, or it may ensue without apparent cause. Though narcolepsy occurs without cataplexy the reverse is extremely rare. This association of the two conditions at once suggests a common pathogenesis, but the muscular atonicity characterizing the cataplectic attack cannot be explained upon any physiological basis. An interesting speculation has been made by Wilson. By comparing the attacks to the defense reaction of certain animals whereby they fall into immobility when frightened, he suggests for them a certain biological significance, namely, that they are the relic of a primitive reaction uncovered by disease.

⁴ This should not be confused with catalepsy, an entirely different condition (p. 919).

CHAPTER LXIX

THE CEREBRAL CORTEX. THE PHYSIOLOGY OF SPEECH AND SOME OF ITS DISORDERS. APRAXIA AND AGNOSIA. EPILEPSY. HEADACHE

MINUTE STRUCTURE OF THE CORTEX

The human cerebral cortex has a total area of about 220,000 square millimeters; not more than a third of this lies upon the free surface or crown of the convolutions. The remaining two-thirds of the gray mantle of the cerebrum occupies the walls of the sulci. On the basis of cellular structure the major part of the cortical gray matter is divisible into *six layers or laminae*. These layers do not show identical histological appearances throughout the extent of the cortex. Characteristic differences in the depth of the individual layers and in their cellular components are found in the various regions. The six layers from the surface inwards with a general description of their cellular features as given by Economo¹ follows (see fig. 375).

I. MOLECULAR (OR PLEXIFORM LAYER). In this, the most superficial layer, the terminal filaments of numerous axons and dendrites form a dense felted network. Its cells are sparse; they are small (4 to 6 μ) and pear-shaped or fusiform.

II. EXTERNAL GRANULAR LAYER consists of large numbers of small round, polygonal or triangular cells closely packed together. Nerve fibers are scanty.

III. PYRAMIDAL CELL LAYER. Medium-sized pyramidal cells are contained in the outer part of this layer; pyramidal cells of larger size and more sparsely distributed are present in the deeper part. It is customary, therefore, to subdivide this layer into an outer and an inner portion; Campbell refers to them as separate layers.

IV. INTERNAL GRANULAR LAYER resembles the external granular layer, being composed of masses of small round granule-like cells. Unlike the external granular layer it is rich in medullated nerve fibers. Its depth is greatest in the calcarine cortex where it gives rise to the well-marked line of Gennari.

V. GANGLIONIC LAYER (or internal pyramidal layer) consists of pyramidal cells of graded sizes. This layer is particularly well-developed in the precentral (motor) cortex where giant pyramidal cells (Betz) are conspicuous. Its deeper strata contain a dense network of myelinated fibers.

VI. FUSIFORM CELL LAYER, in contact with the white matter, is composed of closely packed small spindle-

shaped cells which lie with their long diameters perpendicular.

It should be emphasized that the foregoing more than a general description of the histological structure of the cortex and that marked regional differences exist. Even the lamination itself is a feature common to the entire cortex. In one-twelfth of the cortical area shows little or no lamination; this portion, which is called the *isocortex*, comprises the cortex of the olfactory (i.e., the pyriform area and the hippocampal, supracallosal and olfactory gyri, etc.). The laminated cortex, which in man constitutes the remaining eleven-twelfths and in animals is a much smaller fraction of the whole, is called the *isocortex*.

Over the greater part of the frontal, occipital and temporal lobes the six layers show only minor regional peculiarities. Certain other regions possess distinctive features of a pronounced nature. In the cortex of the precentral gyrus, for instance, both granular layers (II and IV) are shallow, but encroached upon by the expansion of the pyramidal layers III and V. In the deep part of layer III this area are situated the characteristic giant cells of Betz (60 to 80 microns in their longest diameter) (see below). These cells give rise to the fibers composing the corticospinal (pyramidal) tracts. In the frontal cortex in front of the motor area (premotor and frontal association areas [9, 10, 11, and 12]) the granular layers are also inconspicuous but the cells of Betz are absent.

In the cortex of the walls of, and surrounding the calcarine fissure—the *area striata* or *visual cortex*—the departure from the typical histological picture is in the reverse direction. That is, the outer granular layers (II and IV) are expanded at the expense of the pyramidal layers (III and V). This *granular* type of cortex, also called from its “dusty” appearance under the microscope *koniocortex*, is characteristic of sensory areas. The *isocortex* is present, though to a less fully specialized degree than in the visual cortex, in the post-central gyrus and in Heschl's gyrus (auditory cortex, p. 8).

Upon gross examination of a section of the brain two lighter bands can be seen in the cortex again.

¹ For a detailed description, this author, or the earlier works of Campbell and of Bolton, should be consulted.

darker gray matter. These are produced by the fibers running parallel to the surface of the convolutions. They are known respectively as the outer and inner bands of Baillarger. In the precentral area the outer band is broad and prominent and is usually referred to as the band of Gennep.

THE FRONTAL LOBE

Area 4 lies in front of the central (Rolandic) fissure and comprises in man a variable extent of the precentral convolution. It contains the giant pyramidal cells of Betz which give rise to the corticospinal (pyramidal) tracts. It is the center for

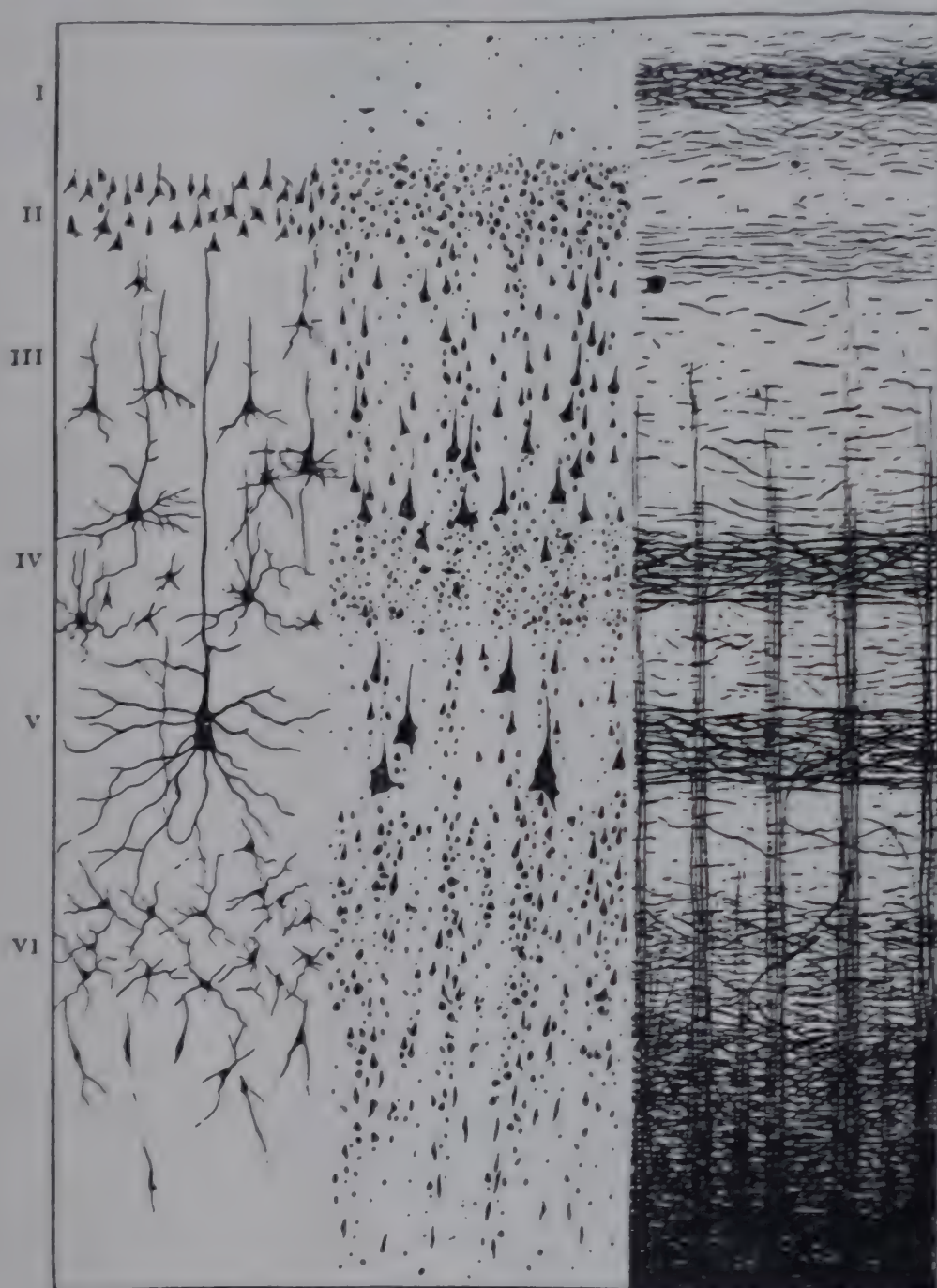


Fig. 375. Area 4 of the human precentral region. Left, neuronal impregnation (Golgi); middle, Nissl cell stain; right, myelogenous stain. Note that the dendrites of the Betz cells (Vth layer) extend to the outer cortical layers (from Fulton after Brodmann).

of Vicq d'Azyr, who had described it previously. The inner band is absent in this area.

LOCALIZATION OF FUNCTION IN THE CEREBRAL CORTEX

Perster, following the numerical terminology of Brodmann and the Vogts, divides the cerebral cortex into several functional areas. Subordinate areas are indicated by letters. Only the more important of these areas will be given (see fig. 376).

voluntary movement, and for this reason is commonly referred to as the *motor area*. Electrical stimulation of parts of this area causes the movement of groups of muscles, different zones within it being correlated with definite muscle groups on the opposite side of the body. The movements induced by electrical stimulation are initiated in the fifth cortical layer and presumably in the giant pyramidal cells of Betz; destruction of the overlying layers by the method of thermo-coagulation

does not prevent the motor response (Dusser de Barenne). The cells controlling the muscles of the foot lie at the upper limit of the motor area. The area for the foot extends on to, or may be situated entirely upon the mesial surface of the hemisphere. Below the foot area lie, in order from above downwards, areas for the leg, thigh, trunk, shoulder, arm and hand. The area 6a α (see below) encroaches upon the center of the motor area dividing it into an upper and a lower half. Area 4 from above downwards controls, respectively, the mus-

possesses extrapyramidal projections (to striatum, etc.) and is in communication with the premotor area through intracortical connections.

Area 4s. This is a narrow band of cortex known as the "strip" area of Hines, lying between areas 4 and 6. Its cytology differs from area 4 in that the giant pyramidal cells of Betz are sparse and scattered. It is looked upon as transitional in cellular structure between areas 4 and 6. Electrical stimulation of this area causes inhibition of contractions of the limb muscles on the opposite

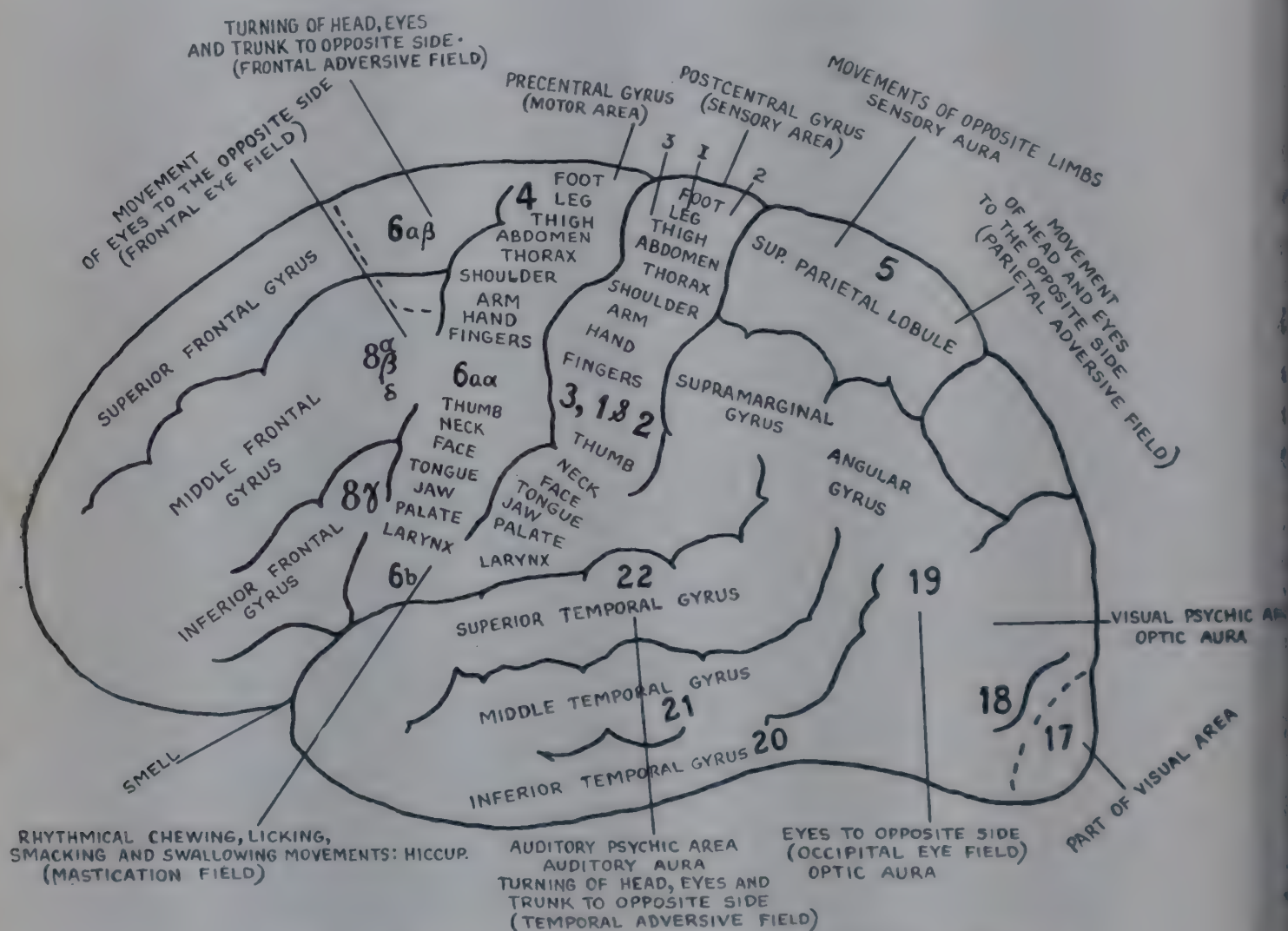


FIG. 376. Showing cortical areas (in part from Foerster and Penfield).

cles of the thumb, neck, face, tongue, jaw, palate and larynx (fig. 376). The representation in the motor cortex of parts such as the hands, lips, tongue and larynx that are capable of complicated or precise movements is much larger in extent relatively to the mass of muscle involved than is that of the neck, trunk, lower limbs, etc. The motor responses caused by the stimulation of area 4 are isolated or discrete in character, that is to say, with a suitably weak stimulus a movement involving a small group of muscles or even a single muscle can be evoked. Area 4, as well as projecting to the spinal cord (pyramidal or corticospinal tracts), also

side of the body; the threshold of excitation of area 4 is also raised.

Area 6 is that part of the cortex lying anterior to the precentral convolution from which complicated apparently purposeful movements of a more generalized type can be elicited by strong electric stimulation. Movements of a more discrete character, though never so discrete as those originating from area 4, can also be evoked from area 6 by weak stimulation during light anesthesia. Area 6 is divided into an upper and a lower part (areas 6a and 6b respectively, see diagram, fig. 376). Area 6a is now generally known as the *premotor area*.

it is subdivided into an upper and anterior and a lower and posterior portion. The former is designated area 6a α , the latter as area 6a β .

Area 6a β lies in front of the upper part of area 4. Its electrical stimulation results in movements which turn the eyes, head and trunk towards the opposite side (adversive movements) accompanied by movements of extension or of flexion of the contralateral limbs.

Area 6a α , as already mentioned, lies in man in the center of the precentral gyrus, splitting the motor area into an upper and lower region. In the monkey and ape the precentral gyrus is not divided in this way, the motor area (area 4) being continuous throughout the latter's extent. Faradic stimulation of area 6a α is followed by adversive movements similar to those arising from the stimulation of area 6a β .

Area 6b occupies the lower extremity of the precentral gyrus. Upon electrical stimulation coördinated rhythmical movements of the jaws, tongue, pharynx and larynx occur, resulting in licking, swallowing, grunting or hiccoughing.

These areas lying in front of the motor cortex differ physiologically from the latter in that the responses elicitable by electrical stimulation are usually of a more general and purposeful character, although as just mentioned movements of a more discrete character may also be evoked. They also require, as a rule, a much stronger stimulus for their excitation, a faradic current usually being necessary. Area 6b, however, can be excited by a galvanic current, and the rhythmical movements which result outlast the stimulus. The premotor area is believed to be a region wherein the synthesis of the more complicated voluntary movements and postural adjustments are carried out. It is therefore looked upon as the highest or third level of motor control, the motor area and the spinal centers representing, respectively, the second and first levels. (See page 890.)

The histology of the cortex of area 6 is similar to that of the motor area except for the important fact that the large pyramidal cells of Betz are absent from the fifth cortical layer. Smaller pyramidal cells, evidently motor in function, are seen in this layer. The fibers of area 6, therefore, are extrapyramidal. They descend through the anterior part of the internal capsule but their subcortical connections are far from being fully known; it seems clear, however, that fibers pass from the premotor area to the corpus striatum, red nucleus and the substantia nigra. The premotor area is therefore regarded as an important cortical center for

the corticostriatonigral system (p. 874). A few fibers, according to Hoff and Kennard, pass without interruption to the spinal centers in association with the pyramidal fibers. The premotor area also apparently gives rise to the frontopontine tract, and through this almost certainly projects to the cerebellum. Area 6b on the left side is intimately concerned with the mechanisms of speech.

Kinesthetic impulses are conveyed to areas 4, 4s and 6 from the lateroventral nucleus of the thalamus which receives them from the periphery via the spinocerebellar tract and cerebellum.

Area 8 occupies the posterior parts of the second and third frontal convolutions. Electrical stimulation of the upper part of this area causes a conjugate movement of the eyes to the opposite side (frontal eye field). If the stimulation is strong the head is turned in the same direction and the eye movements are jerking or clonic in character. Opening and closing of the lids, dilatation of the pupil and lacrimation of the opposite eye may also result.

The *prefrontal area* or *frontal association areas* (9, 10, 11 and 12) include all of the cortex lying anterior to areas 6 and 8. Areas 9 and 10 occupy the convexity and medial aspect of the frontal region, areas 10 and 11 its orbital aspect.

The results of extirpation of frontal areas

In lower vertebrates, e.g., fish, amphibia and birds, the rudimentary cortex plays a very subsidiary rôle in the control of motility. Subcortical and phylogenetically older portions of the cerebrum (corpus striatum and thalamus) are dominant (p. 874). The frog after cortical extirpation behaves in an almost normal fashion; and even the dog or cat walks a short time after the cortex has been removed, most of the postural reactions being retained (thalamic animal). The motor area of these animals is much less easily excited by electrical stimulation than is that of the monkey, ape or man, and the excitable area is much smaller in extent.

In monkeys, as shown by Lashley, destruction of the greater part of the precentral gyrus (motor area) does not abolish the animal's ability to perform acts previously learned, such as opening a hasped box to obtain food.

Fulton and Keller found that in the monkey after bilateral excision of the cortex of area 4 governing the lower limbs hip flexion was possible almost immediately after recovery from the anesthetic. Flaccid paralysis of the muscles of the knee, ankle, elbow and wrist persisted for three or four days,

but after this, voluntary power gradually returned, together with the tendon jerks. The proximally situated muscles recovered first. The finer movements of the digits returned slowly and incompletely. In the chimpanzee the results were similar but the loss of power was more profound and recovery slower. A positive Babinski without "fanning" of the toes was present. *In no instance was there permanent spasticity, which is usually considered in man to be due to a lesion of the motor area or corticospinal (pyramidal) pathway, observed after removal of the motor cortex alone.* Removal of area 6 or of area 4s ("strip" area), on the other hand, was followed by spasticity, increased tendon jerks, involuntary forced grasping and groping, and loss of the ability to execute complicated movements of the fingers. Rossolimo's sign (p. 873) and a positive Babinski, with fanning of the toes, appeared. Removal of the motor area on one side, followed by excision of the corresponding premotor area resulted in pronounced spasticity and loss of voluntary power in the contralateral limbs, accentuation of the Babinski response and fanning of the toes. The condition resembled the hemiplegia which in the human subject results from a lesion in the internal capsule. Fulton and his associates conclude that the sign of Babinski without fanning of the outer toes (p. 872) is indicative of a purely pyramidal lesion, the presence of the fanning component being an index of a premotor injury.

The connections of area 4 with the premotor area and with subcortical centers (corpus striatum, pons, etc.) render it impossible by means of a cortical lesion to produce effects attributable purely to the destruction of corticospinal projections. But the corticospinal fibers form two compact bundles—the pyramids—lying on the anterior aspect of the medulla (p. 862). Marshall and later Tower sectioned the pyramid of one side in cats and Tower and Hines in the monkey, thus accomplishing the dissociation of pyramidal from extrapyramidal effects. Section of the pyramid of one side in the medulla at the level of the trapezoid body resulted in paralysis of discrete movements of the opposite side, somewhat less in degree than that caused by ablation of area 4 itself. Larger movements (e.g., adverse) and, with strong stimulation, epileptiform responses were still elicitable. The most important finding was the absence of any sign of spasticity in the affected muscles, indeed there was some degree of hypotonicity (flaccidity). Ablation of area 4, especially of its anterior part, after pyramidal section increased the paralysis and induced hypertonus of the muscles. Stimulation of area 4

caused inhibition of the extensor tone of the paralyzed limbs, as well as of the sound (i.e., ipsilateral) limbs. Stimulation of area 6, on the other hand, induced hypotonicity of the flexor muscles, the grasp of the hand, for example, undergoing relaxation.

From the foregoing account of the various experimental results in this difficult field the following inferences may be drawn. (1) The pyramidal system (projections from area 4) governs the fine discrete or isolated motor responses, whereas the extrapyramidal system (projections from areas 4s, 4s and 6, but especially from the latter) are concerned with the larger coordinated responses (e.g., the so-called adverse movements). (2) Areas 4s and 6, particularly the latter, exert an inhibitory influence through extrapyramidal paths upon movements (mainly contralateral) governed through the pyramidal tracts. Extrapyramidal projections from areas 4s and 6 inhibit the tone of the flexors (e.g., relaxation of the grasp of the fingers); those from area 4 inhibit the extensors. (3) Pyramidal function includes as well a tonic action upon the spinal centers. Interruption of pyramidal pathways results in hypotonicity of the paralyzed muscles, whereas lesions of extrapyramidal paths cause spasticity. These conclusions have important clinical implications. The spastic state of the affected muscles in hemiplegia, for example, has been generally considered to be indicative of a destruction of pyramidal pathways. It appears, however, that interruption of extrapyramidal fibers, in their course through the internal capsule in close association with the corticospinal tracts, is responsible for the hypertonicity of the muscles. (4) The premotor area is capable of initiating certain relatively gross muscular acts quite independently of the motor cortex (area 4). Nevertheless, in the intact animal the two cortical regions are apparently closely correlated in function, the discrete movements of area 4 being integrated, through its connections with area 6, into the larger more complex movements involved in acts of skill and postural adjustments.

Fulton and his colleagues describe certain motor disorders in man which they consider to be characteristic of a lesion of the premotor area. These, which have been grouped under the term "*the syndrome of the premotor cortex*," are as follows: (a) awkwardness in the performance of delicate manual acts, e.g., buttoning a collar, sewing, etc., but little early loss of power in the execution of gross movements, (b) spasticity and increased tendon jerks, (c) forced grasping and groping (p. 892), late

appearance of weakness of the handgrasp and impairment of gross movements, and (d) autonomic disturbances. These effects are of course on the side of the body opposite to the lesion.

Unilateral excision of area 8 is followed in the monkey by conjugate deviation of the eyes to the side of the lesion and, during locomotion, rotation of the body to that side. A visual defect in the form of failure to recognize objects in the opposite monocular halves of the visual fields—a *pseudomianopia*—results. When area 8 is destroyed on both sides the animal does not react in a normal manner to visual stimuli. It may appear to be blind for it walks into or stumbles over obstructions in its path, and tends to stare straight ahead with an immobile “wooden” expression (see Kennard and Ectors). Yet, an animal will follow an object with its eyes and will seize anything offered to it though failing, apparently, to recognize it or to understand what to do with it.

Unilateral or bilateral removal of the *prefrontal* area (areas 9 and 10, 11 and 12), i.e., the portion of the frontal lobe lying in front of the premotor area causes no motor defect either in the monkey or man. Unilateral removal of the human prefrontal area is without any outstanding effect. The mental processes are impaired only to a minor extent. Some loss of initiative and mental alertness, and lowered ability for arithmetical calculations may be the sole result of the operation. Memory, judgment and intellect often show little or no deterioration. Removal of the prefrontal area of the dominant hemisphere (i.e., the left in right-handed and the right in left-handed persons) tends to produce somewhat greater alterations in character or intellect than does a similar operation on the non-dominant side. But even the bilateral excision of prefrontal areas is followed by surprisingly little mental defect. In an operation for the eradication of a tumor, Dandy excised the frontal lobes on both sides in front of the premotor areas (reported by Brickner). The subject of this extensive extirpation appeared of normal intelligence upon a casual acquaintance. It is reported that for an hour he toured the hospital with two visiting neurologists who failed to notice in him any mental abnormality. A more intimate knowledge of the patient, however, revealed very definite defects of character and mentality. His mental age was about thirteen years; his intelligence quotient eighty. The main features shown by this subject and which may be taken generally as representative of the effects of bilateral prefrontal destruction are as follows:

(1) *Lack of restraint* leading to boasting, self-aggrandizement, hostility, aggressiveness.

(2) *Distractibility*—difficulty in fixing attention.

(3) *Flight of ideas*, puerile fantasies, emotional instability, facetiousness, punning.

(4) *Lack of initiative*.

(5) *Impairment of memory* for recent events but not for remote events.

(6) *Impairment of moral and social sense*, loss of love for family.

(7) *Failure to realize*, or indifference to, the seriousness of his condition, and a sense of well-being (euphoria).

Among some of the other manifestations which may follow a prefrontal defect are: (a) increased appetite and loss of weight, (b) impaired control of the sphincter of the bladder or rectum, (c) disturbances of orientation in time and space, and (e) tremor.

Chimpanzees which have had both prefrontal areas (9, 10, 11 and 12) removed show restlessness and are easily distracted, though they remain alert and evince a keen interest in things around them. Jacobson has reported that after this operation the animals appear to be immune to experimental neurosis (p. 912) an observation which forms the basis for the surgical treatment of patients suffering from certain types of psychoneuroses namely, the severing of fibers connecting the frontal association areas with subcortical centers (probably the thalamus).

The frontal lobes and intelligence

The development of the frontal lobes bears in general a direct relationship to the level of an animal in the phylogenetic scale and to its intelligence. This has led to the belief that this part of the cerebrum is the seat of the intelligence of animals and the “center” or “organ” of the mind of man. Within this region those processes underlying intellectual, moral and emotional attributes were supposedly carried out. Extirpation experiments, however, show decisively that the prefrontal area cannot be looked upon as a region where these higher mental qualities reside exclusively. Intelligence depends upon a knowledge of the external world received through various channels. Visual, auditory, somesthetic perceptions, etc., are received and stored as memories in cortical areas situated in the occipital, temporal and parietal lobes. Tracts of association fibers link together in turn these several primary areas; sensations of various types are thereby brought into relationship, and synthesized into more complex memories.

Thus, as time passes, the fabric of our experience is woven in patterns of greater and greater intricacy.

It is probable that the prefrontal area merely represents a region of relatively high associative or synthetic capabilities. After its bilateral removal the cerebrum deprived of the synthesizing faculty of this region is incapable of the more elaborate association of those experiences required for the formulation of abstract ideas and more accurate judgment, and for the guidance of conduct in conformity with social customs. Nevertheless, synthesis at somewhat lower levels is still possible of achievement through the remaining cerebral tissue. Mental capacity according to this conception is therefore a function of the cerebral cortex as a whole rather than of any particular region. The *quantity* of tissue removed rather than its *location* is the more important factor in determining the degree of mental impairment which will result. (See Lashley.) It may be mentioned in this regard that the symptoms which are observed in prefrontal lesions can all be accounted for by a reduction in associative ability. Bolton has also shown that in amentia and dementia the degeneration of the cortical layers is not localized to any particular region but is distributed over the hemispheres.

THE CEREBRAL CORTEX AND THE AUTONOMIC NERVOUS SYSTEM. The lower levels of the autonomic system (e.g., hypothalamus) are undoubtedly under cortical influence. Lesions of the cortex (areas 6 and 4) in man are associated with vasomotor changes in the parts of the body affected by the cerebral injury. Similarly autonomic effects have been noted following ablations of these cortical areas in monkeys and chimpanzees. Shivering, sweating, pilomotor effects and gastrointestinal disturbances are also frequently associated with cortical lesions. The effect upon blood pressure and heart rate can be evoked by stimulating of area 6a and changes in respiration by stimulating area 6b.

Grasping movements and tonic innervation

The weakness on the opposite side of the body which occurs in lesions of the premotor area is not uncommonly associated with a group of phenomena to which various terms have been applied, e.g., "forced grasping and groping," "grasp reflex," "tonic innervation" and so forth. A description of these phenomena follows.

(1) Merely touching the skin between the finger

and thumb with a pencil results in slow flexion of the fingers. If the stimulating agent is withdrawn gently without disturbing the position of the patient's fingers no tightening of the grasp results but his hand and arm sometimes move through space (grobe) in the direction of the moving object, as if drawn by a magnet.

(2) When an object is placed in the paretic hand of the patient the fingers close slowly and gently around it, but any attempt made by the observer to withdraw the object often results in its being grasped more firmly. Nevertheless, when the patient clenches his empty fist he can relax the fingers again without difficulty.

(3) Any attempt to bend the arm or leg is met by an active resistance exerted by the antagonist (stretched) muscles; this differs from the resistance offered by the ordinary spastic limb in that there is no sudden giving way with a "clasp-knife effect."

Walshe and Robertson have made a critical study of these phenomena and find that they are separable into two distinct components: (a) the *grasp movement* and (b) *tonic innervation*.

The *gentle grasp* and the *groping movement* just described (see (1) above) are voluntary and not reflex acts. That is to say, though they are automatic in nature and are taken to indicate deterioration of the psychomotor functions, the patient can prevent their occurrences if asked to do so. They disappear in stupor or in coma. The gentle grasping movement follows tactile stimuli alone or visual and tactile stimuli acting together. The groping movements can be elicited by visual stimuli alone but not by tactile stimuli alone.

Tonic innervation (see (3) above) is a stretch reflex (p. 822). The *strong grasp* (2) which results when an attempt is made to remove an object from the hand is simply one phase—an incident—of this reflex. It is quite distinct from the gentle grasp movement. It results from the passive stretching of the flexor muscles of the fingers caused by the observer's attempt to extricate the object. It occurs in the unconscious patient.

Richter and Hines produced the "tonic grasp reflex" in adult monkeys by removal of the premotor area (fig. 377). Excision of the motor areas or the prefrontal areas from both hemispheres did not cause the effect. A similar reflex is present in normal infants, Robinson showing that in them it is sufficiently strong to suspend the body from a bar for 2 minutes. A grasping reflex has also been described for the foot in lesions of the premotor cortex; it occurs in the normal infant up to the end of the first year and is said to occur in 50 per cent

Mongolian idiots. It is elicited by stroking the sole.

THE PARIETAL LOBE

The somesthetic area

The *postcentral gyrus*, i.e., the band of cortex lying behind and including the posterior lip and

foot are recorded, below this are placed in order, sensory areas for the leg, thigh, trunk, shoulder, arm and hand. Cushing, for example, stimulated different parts of the area in a conscious patient; sensations on the contralateral half of the body were experienced, their locations bearing a constant relationship to the point stimulated. Dusser de Barenne discovered that the application of a

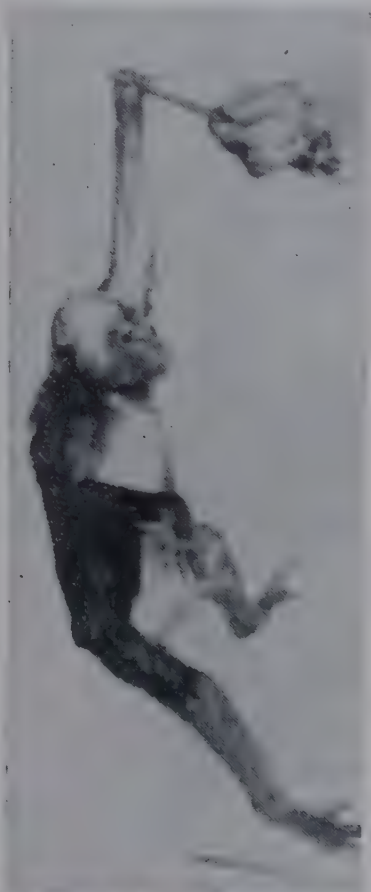


FIG. 377. Upper photograph; a young female baboon after bilateral extirpation of motor and premotor areas, showing grasping of left hand and spastic posture of other extremities. (From Fulton and Kennard.) Lower photograph; *left*, infant showing the suspended grasping reflex, *right*, infant showing resistance to removal of rod from the hand (from Chaney and McGraw).

All of the fissure of Rolando, is sensory in function. Excisions of the cortex from this region are followed by disturbances of cutaneous and somesthetic sensations on the opposite side of the body. As in the case of the motor area different levels of the postcentral gyrus are correlated with definite regions of the body (fig. 378). Thus, in the upper part of the gyrus, sensations from the

strychnine solution to the postcentral gyrus in monkeys caused sensory effects (paresthesias, hyperesthesia and hyperalgesia), most marked on the opposite side of the body but also on the same side. Deep sensibility is represented almost entirely contralaterally.

The sensory area of the cortex (*somesthetic area*) is not confined to the postcentral gyrus but em-

braces as well the *superior parietal lobule*, the *supramarginal gyrus* and the *angular gyrus*, and, for some type or types of sensation at least, e.g., proprioceptive, extends forward into the *pre-central gyrus*.

The method of strychninization for mapping the sensory representation in the cortex has its limitations, the diffuse action of the drug rendering strict localization impossible. Moreover, strychninization evokes maximum sensory responses, the finer differences in sensation being blurred or obscured. Marshall, Woolsey and Bard have used a method to map out the cortical representation of tactile sensibility in monkeys, based upon the fact that impulses set up by stimuli applied peripherally can be recorded as action currents from the surface of the hemisphere (fig. 000). They found tactile sensations represented contralaterally in the post-central gyrus (areas 3, 1 and 2). Bilateral repre-

texture, etc., and of the positions of our limbs in space. Through cortical activity a particular sensation is subjected to critical appraisal, compared with or related to another simultaneous or consecutive sensation; thereby, its intensity and nature are accurately judged. Thus, according to Head, the somesthetic area of the cortex, through the integration of the primary sensations, becomes endowed with three discriminative faculties. These are:

(a) **SPATIAL RECOGNITION**—the appreciation of spatial relationships in space, e.g., the recognition of position, passive movement of the limb, the discrimination of points, and the localization of a point which has been touched.

(b) **RECOGNITION OF THE RELATIVE INTENSITY**—different stimuli, e.g., that one object is warmer or colder than another, or that one stimulus is more painful than another.



FIG. 378. Action potentials recorded from postcentral gyrus during tactile stimulation of points on hand. (Part of figure from Marshall, Woolsey and Bard.)

sensation was not observed, except occasionally, for the face. In no instance was evidence obtained for the precentral representation of this sensation.

All somatic sensory impulses ascend in the medial fillet to the thalamus. This nuclear mass is the final destination of crude sensations (protopathic, see p. 803). The finer sensations of touch and temperature and the sense of position and movement are relayed to the cortex by fibers which ascend through the internal capsule and corona radiata. The function of the somesthetic cortex, according to the views of Head and his associates, is not, however, simply to record these several primary sensations. Its activity lies in the psychological sphere; cortical sensation, to quote these observers, is one of the "elementary processes of the mind." The somesthetic area brings its discriminative and synthesizing abilities to bear upon the primary sensations which it receives, and from these are formed our perceptions of the qualities of external objects, such as their size, shape, weight,

(c) **RECOGNITION OF SIMILARITY AND DIFFERENCE**—appreciation of the shape, relative size and texture of objects, and the estimation of their weights. These abilities are frequently grouped under the term *agnosis*.

In a lesion involving the somesthetic area or other, but usually all three, of these faculties are disturbed. Yet as a rule they are not all affected to the same degree. Spatial recognition shows the greatest disturbance the farther forward the lesion lies in the somesthetic area. Appreciation of intensity is disturbed most by lesions involving the foot of the postcentral gyrus and the supramarginal and angular gyri. Recognition of similarity and difference is affected most by lesions involving the middle of the postcentral gyrus.

In the lesion confined to the cortex, the impulses ascending from the thalamus and conveying the primary sensations, e.g., light touch, temperature, passive movement and position, etc., upon which the cortical faculties depend, are intact and

tions are appreciated. The subject of such a has difficulty, however, in bringing the vary discriminative ability to bear upon the tion in order to judge it, and he is unable to esize different sensations into a composite sion which will enable him readily to identify ject. When tested, he is uncertain in his rs, which tend to vary from moment to nt, and it is difficult for the examiner to nine the threshold for a given sensation. gh he recognizes that an object is warm, he t say whether it is warmer or less warm than er object which he has felt previously or at me time. Similarly, although he knows a limb has been moved, he cannot say into osition it has been placed. He responds to stimuli, but also with inconstancy, and he is even less consistent in his answers when the th of the stimulus is increased. He cannot the point touched and may respond when not d (hallucination of touch). The weights ects placed upon the hand cannot be esti-, and a fabric (e.g., silk or tweed), though be smooth or rough cannot be recognized. for example, a piece of tweed is placed in d the patient may say, "I feel it, it is rough, ave no idea what it is."

tonia may also be a symptom of lesions of sory cortex; it corresponds in distribution to as of the sense of position and passive ent.

cortex at the lower end of the somesthetic ongue and face area) appears from the of Bornstein to be the *center for taste*. ea lies adjacent to the motor cortex govern- e muscles of mastication. It has been ly taught, but on doubtful evidence, that ter for taste lay close to that for smell, , in the region of the hippocampal gyrus. ation of this sense in the parietal lobe by ein is based upon a study of war wounds of in.

SUBCORTICAL LESION of the sensory path- e., from the thalamus to cortex) disturb- n the cortical faculties obviously must since many of the impulses from which aculties are integrated will fail to reach stination. The defects, however are much they are in terms of the primary sensations, ccordance with the three cortical faculties. s not the uncertainty and inconstancy of e characteristic of lesions of the somesthetic The patient either feels a sensation or he t, and gives the same answer each time a

given stimulus is repeated. The loss of the indi- vidual sensations is often severe but when the particular stimulus is increased a response can usually be obtained.

Motor effects of a generalized type are produced by electrical stimulation of the posterior part of the superior parietal lobule (area 5, parietal ad- versive field). These are movements of the head and eyes to the opposite side. Stimulation of the angular gyrus causes conjugate deviation of the eyes to the opposite side.

Attacks of Jacksonian epilepsy, due to lesions of the sensory cortex, may be preceded by sensory aurac—comprising pricking sensations, "pins and needles," sensation of cold, etc.

THE TEMPORAL LOBE. THE CENTERS FOR SMELL AND TASTE

The primary cortical center for hearing is situ- ated in the transverse gyrus of Heschl lying in the floor of the lateral cerebral (Sylvian) fissure, and an adjoining small area of the superior temporal gyrus. Fibers from the medial geniculate body reach this *auditosensory* area via the posterior limb of the internal capsule; they constitute the *auditory radiation* (p. 1024). In the audito- sensory area the fundamental auditory sensations—intensity, quality and pitch—are appreciated. The area is bilaterally represented. A large part of the cortex of the superior temporal gyrus con- tiguous to this primary area is *auditopsychic* in function. Herein the analysis and interpretation of auditory sensations, and their integration into more complex perceptions take place. The audito- psychic area is mainly unilateral, being on the left side in right-handed individuals and vice versa.

Electrical stimulation of the posterior part of the superior temporal gyrus (area 22) in man causes adverse movements similar to those fol- lowing stimulation of area 6a β .

Fibers descend from the cortex of the temporal lobe to: (a) the *medial geniculate* body and *inferior colliculus*; the former is therefore connected with the auditory area by both ascending and descend- ing paths. (b) The *nuclei of the pons*. These fibers constitute the *temporopontine tract* which traverses the posterior limb of the internal capsule and the outer part of the base of the cerebral peduncle. Through these fibers and the ponto- cerebellar tract the temporal lobe is in communica- tion with the cerebellum. The temporal lobe is connected also with the thalamus by both ascend- ing and descending fibers.

The CENTER FOR SMELL is situated in the uncus and the anterior part of the hippocampal gyrus (pyriform area). Owing to the close relationship of these parts of the rhinencephalon to the temporal lobe, lesions of the latter (e.g., tumor, abscess, etc.) are not uncommonly associated with disturbances of the olfactory sense.

A LESION OF THE TEMPORAL LOBE may result in—

(a) *Aphasia*. In a series of left temporal lobe lesions reported by Frazier and Rowe this disorder was present in 36 per cent. Others have reported higher percentages (e.g., Kolodny, 57 per cent).

(b) *Auditory disorders*, deafness, tinnitus (ringing or buzzing, etc.) or auditory hallucinations (e.g., hearing voices) may occur.

(c) *Olfactory and gustatory disorders*, impairment or loss of smell, or olfactory hallucinations, the subject imagining he smells some disagreeable odor. Taste may be defective or there may be disagreeable gustatory sensations.

(d) *Dreamy states*. The subject experiences a sensation of unreality in which hazy memories of long past events are awakened. Such states are due to involvement of the region of the uncus and are sometimes on this account called uncinata attacks. In normal persons certain odors arouse a milder but somewhat similar sensation.

(e) *Disturbances of memory*.

(f) *Hemianopia* (pp. 1007, 1008).

(g) *Epileptiform seizures*. The convulsions may be ushered in by adverse movements (fig. 376) and are frequently preceded by an auditory, olfactory or gustatory hallucination (aura), or by the dreamy state. The fit is sometimes precipitated by a sudden noise.

THE OCCIPITAL LOBE

The gray matter forming the walls of, and surrounding the calcarine fissure (on the medial aspect of the occipital lobe) constitutes the primary cortical center for vision—the *visuosensory area*. From the broad stripe of Gennari which can be seen with the naked eye this area is commonly known as the *area striata* or, following the numerical terminology, as area 17. It has been considered in more detail on page 1009. Its histological features have already been touched upon (p. 886). The *visuopsychic area* wherein the visual sensations are interpreted and integrated into more complex perceptions is contiguous to the *area striata* lying on the lateral aspect of the occipital lobe (area 18).

Stimulation of the anterior part of the lateral surface of the occipital lobe causes conjugate deviation of the eyes to the opposite side (occipital field, area 19).

THE PHYSIOLOGY OF SPEECH AND SOME OF ITS DISORDERS

The first stage in the development of speech is the association of certain sounds—(words)—with visual, tactile and other sensations aroused by objects in the external world. These associations are “stored” as memories. After definite meanings have been attached to certain words, pathways between the auditory area of the cortex and the motor area for the muscles of articulation become established, and the child attempts to formulate and pronounce the words which he has heard. This act of verbal expression involves the coördinated movements of a large group of respiratory, laryngeal, lingual, pharyngeal and labial muscles. Later, as the child is taught to read, auditory speech is associated with the visual symbols of speech, and finally, through an association between these and the motor area for the hand, the child learns to express his auditory and visual impressions by the written word.

APHASIA

This term is applied to those disorders of speech resulting from defects in the nervous mechanism underlying the comprehension and use of symbols (words, numerals) for the formulation, transmission and reception of ideas. Aphasia is not simply a defect in the pronunciation of words as a result of the paralysis of the muscles of articulation. The innervation of the latter—motor area, corticobulbar fibers, cranial nuclei or peripheral nerves—is not necessarily affected. The defects in aphasia involve higher neural levels; they lie in the psychical sphere.

Before giving Head's views on aphasia, a short account of previous ideas on the subject may be helpful to the reader.

The views of the neurologists of the 19th century had the merit of simplicity. These observers, whom Head refers as the “diagram makers,” conceived of the language faculty as built up of several separate components. Each of these, supposedly, was represented by a definite anatomically circumscribed area of the cortex, and could be affected independently of the others.

Two of these centers were *sensory* and two *motor*. All four were linked together by association tracts.

such a scheme, memories of spoken words were stored in the superior temporal convolution—the ditopsychoic center; the cortex in the region of the angular gyrus was the repository of visual word memories. These two receptive areas comprised what was referred to as Wernicke's zone. The pair of motor centers, i.e., those presiding over the coordinated movements concerned in vocalization and writing were called respectively the glossokinesthetic and cheirokinesthetic centers. The former was located in the posterior part of the 3rd frontal convolution; the latter in the hind part of the 2nd frontal convolution, in most instances on the left side. Diagrams were drawn confidently to show these four centers with their interconnections, and the type of aphasia which would result from the destruction of one or other component part of the neural mechanism. Broca (1861) believed that *motor aphasia* (see below) was the result of a lesion of the glossokinesthetic area (Broca's area), especially of the left side. Defects of the ability to write—*agraphia*—were held to be the result of the involvement of the cheirokinesthetic center. *Sensory* aphasias were classed as *auditory*—loss of the comprehension of audible speech—and *visual*—the inability to understand written or printed words. The former was held to be due to injury of the second temporal gyrus; the latter to injury of the angular gyrus. The extreme proponents of this view even considered that every memory, auditory or visual, has its anatomical representation, so that a lesion limited to a small group of nerve cells would cause the loss of only those word memories for which they were regarded as centers.

The different types of aphasia which were recognized may be briefly described.

(a) **MOTOR APHASIA (Broca's).** This term was applied to the type of speech defect in which the patient is almost speechless, but there is no paralysis of the muscles of articulation. Though unable to express his thoughts in words, he can understand what is said to him and can read. He is usually able to utter a few words of an ejaculatory nature, "oh my," "dear me," "damn," etc. Sometimes he is able to say the last words which he spoke just before the onset of his illness, as the oft cited case of the librarian whose only words were, "lists complete."

(b) **AGRAPHIA.** This term indicated that the patient was unable to write though motor speech and the comprehension of written or spoken words were possible. The movements of the hand and other acts were not necessarily impaired.

(c) **AUDITORY APHASIA OR "WORD DEAFNESS"** were the names given to those defects of the language faculty in which the subject, though able to hear, does not understand spoken words. He is as a person listening to a strange language. The power of speech, writing and the comprehension of written or printed words are retained. He may be able to repeat words spoken to him, and instead of answering a question may simply repeat the questioner's words; this phenomenon is called *echolalia*.

(d) **VISUAL APHASIA OR "WORD BLINDNESS" (ALEXIA).** Vision may be unaffected yet the recognition of written words or numerals and the appreciation of their meanings are impaired or lost.

In 1906 these mechanical conceptions of the speech faculty and the production of aphasia were challenged by Pierre Marie. He claimed that there was only one true type of aphasia—sensory aphasia—due to a lesion in Wernicke's zone, and associated with a lowering of those intellectual capacities upon which were based the use of symbols in the expression of ideas. Thus, not only was the comprehension of written or spoken words defective but the ability to solve problems in arithmetic, and to perform certain other mental tasks were impaired. He maintained that the classical motor aphasia of Broca was simply *anarthria* (see below) due to involvement of the motor cortex governing the muscles of articulation plus sensory aphasia, and that a pure motor aphasia, i.e., a defect of speech due to the loss of "motor images" did not exist. Marie denied the existence of isolated cortical centers governing the different aspects of the speech faculty, and attacked the belief that aphasia was the result of the destruction of images—motor, auditory or visual—in such specific areas. He reexamined the brains of Broca's first two patients, which had been preserved in the Musée Dupuytren in Paris, and found no confirmation of the view of Broca that the posterior part of the third frontal convolution was necessarily involved in aphasia. In the first brain, the lesion was not confined to Broca's area but involved Wernicke's zone. The second specimen did not show a circumscribed lesion but, on the contrary, a generalized wasting; the posterior part of the third frontal convolution was not especially implicated.

The terms in the classification given above, e.g., motor aphasia, agraphia, "word deafness," etc., are still sometimes employed, but it is understood that they refer to the outstanding features of a

given case rather than that they denote clear-cut types.

Head's classification of the aphasias

Head's views, based upon an exhaustive study of patients suffering from gunshot wounds of the cortex, are also strongly opposed to the conception of the speech faculty being dependent upon circumscribed anatomical centers. He considers speech to be a highly integrated cortical process—a special aspect of intelligence—yet one which can suffer with little lowering of the general intellectual level. The different components of the speech faculty, he decides, cannot be separated from one another by disease. Nor, consequently, can the types of aphasia be classed as “motor” or “sensory,” but in any type deficiencies on both the receptive and the executive side can be demonstrated. Head concludes that aphasia is a state in which the power to use words and other symbols as instruments of thought and expression is affected or, as he expresses it, “aphasia is a defect in symbolic formulation and expression.” The more complicated or abstract the idea which must be understood or expressed, the greater is the difficulty. Thus an aphasic may be able to name *objects* correctly but fails to find the word for a more *abstract idea*, e.g., color. Shown a black object, for instance, and asked to name its color he fails to do so, yet indicates that he recognizes that it is black by saying “what you do for the dead.” An aphasic soldier when shown a red object said, “what the staff wear.”

Head, as a result of an extensive investigation of aphasic patients, devised a series of six tests of graded severity. These tests are briefly as follows:

(1) *Naming and recognition of common objects.* Six objects, e.g., a pencil, key, knife, etc. The patient is asked to name each object as it is pointed out to him. Next he is asked to point to each object as its name is called out. He is then given cards upon each of which the name of one of the objects is written. He is asked to indicate the object named.

(2) *Naming and recognition of colors.* This test is carried out in a manner similar to that described for test (1) except that eight strips of differently colored silk are substituted for the six objects.

(3) *Man, cat and dog test* is designed to investigate the powers of reading and writing in their most elementary forms. The printed words “man,” “cat” and “dog” are employed. The subject is asked to read these words; to write them from dictation; to copy them or to repeat them after hearing them spoken. Pictures of a man, a cat and a dog are also shown and the patient asked to write or to speak their names.

(4) *The clock tests.* The patient is requested to set the hands of a clock in the same positions as those of a similar one set by the observer. He is then told to set the clock from verbal or printed commands. Again he is asked to state the time aloud or by writing, of a clock set by the observer.

(5) *Coin bowl tests.* Pennies are placed one in front of each of four bowls. The patient is asked verbally and in writing to place a coin in one or other of the bowls according to their number in the row. He is then asked to give an order himself and to carry it out according to his own words.

(6) *The hand, eye and ear tests.* The patient is requested to repeat the movements of the observer which consist in touching an eye or an ear with one or other hand. When this is done correctly the patient's hand which moves is of course diagonally opposite to the hand of the observer. A much easier form of this test is the imitation of the observer's movement as reflected in a mirror. This simply requires matching without calculation.

The aphasic frequently fails to recognize that when the one hand is brought to his contralateral eye or ear the hand crosses the face. A further part of the test is to ask him to imitate the positions shown in pictures or form upon cards or to carry out the movements from printed and verbal instructions. Finally, he is asked to write down movements made by the observer.

From the results of such tests upon a large number of aphasics, Head divides speech defects into four groups. A brief account of these based upon his description, follows.

(1) **VERBAL DEFECTS.** The outstanding feature is if a defect in the utterance of individual words of all kinds. The power to express an idea in words is practically lost. The patient, however, is not entirely speechless but can usually utter a few monosyllables, “yes” or “no,” etc., or ejaculations and emotional expressions, such as, “damn,” “dear me.” When the disorder is less severe, the words are mispronounced but sentences are correctly constructed. For example, one patient said that he had trouble with “tenical terms” (technical terms) and that he “had *diffulty* in remembering what you do with a skull, *tri-tre-tripine*” (trepan). Another spoke of “*claration* of war by the *Ollie*” (declaration . . . Allies). Another would say “*pyramerad*” (pyramid), “*sissiors*” (scissors) and “*oboid*” (ovoid). Such patients read with difficulty and writing is very defective or impossible. They usually understand printed or oral commands. This form of aphasia resembles the classical motor aphasia described on page 89.

(2) **SYNTACTICAL DEFECTS** (agrammatism or jargon dysphasia). The patient is voluble but speaks a jargon in which, though the individual

words may be fairly accurately pronounced, they are strung into short phrases or badly constructed sentences without articles, prepositions or conjunctions. The ability to read aloud is impaired, and curiously enough such a patient, though he can write a well constructed letter, may be quite unable to read it coherently. Such a one when asked the contents of a letter which he had just written replied, "I cant; I know, I suppose in time, not now, funny thing, why." In other instances the words themselves are often slurred over, mutilated and may be unrecognizable. Speech sometimes resembles "baby talk." Thus one patient when asked what his right arm felt like replied "Tiff-ant from uffer um" (different from other arm). The understanding of ordinary conversation is defective.

(3) **NOMINAL (NAMING) DEFECTS.** In this type of speech disorder the patient has difficulty in finding the right word to express his meaning or in naming a well known object. Such patients will often employ a descriptive phrase in substitution for the word which they cannot recall. For example, a painter when asked to name a series of colors could not say "violet" but instead explained that "it was made with black, red and a bit of blue." Another when asked to tell the time from a clock which had both hands at 12 replied "That's when you eat." These patients can draw from a model either directly or from memory, after it has been shown and then removed, but are usually unable to draw from imagination. They write a coherent letter with difficulty, usually fail to carry out simple arithmetical exercises and confuse the values of coins.

(4) **SEMANTIC² DEFECTS.** A patient suffering from this type experiences little difficulty in articulating speech, can name objects, understands individual words and some sentences, but the general meaning of what he hears escapes him. He often fails to follow his own utterances to an intelligent conclusion, his sentences tailing off as though he had forgotten what he had started out to say. When shown a picture he picks out the details but fails to grasp the meaning which it conveys to others. Such a patient therefore misses the point of a joke whether this is printed, told to him, or is in pictorial form. He fails to comprehend the significance of much that he sees and hears. There is no impairment in the pronunciation of words, though speech tends to be in short jerky sentences, syntax and intonation are not disturbed.

²Semainein = to signify.

Head, though he discards the conception that the neural basis of speech consists of strictly localized anatomical "centers" wherein resides *exclusively* one or other of the speech functions—auditory, visual or motor—believes that regions exist in the cortex "where the progress of some mode of action can be reinforced, deviated or inhibited." These regions constitute foci of integration—convergence points for association paths. Destruction of one or other of such foci or "knots" of association paths will depress *as a whole* the psychological processes underlying speech. The speech faculty is disabled; certain faculties are lost, while others are retained. Yet he points out that it is not logical to conclude that the abilities which remain and those which have been abolished constitute essentially separate and distinct functions from which the normal processes of speech have been synthesized, or that they are represented in specific circumscribed areas. To make a rather crude comparison—a person who has injured his foot, knee or hip, adjusts his locomotor apparatus as best he can. He hops or limps, yet it can not be argued that the hopping or the limping motion which he employs is simply one of the component movements employed in the normal act of walking which the injury has left intact. Nevertheless, the form which the disability assumes is undoubtedly influenced by the site of the injury. The ambulatory abnormality, for example, which results from an injury to the foot is different from that resulting from injury to the knee or hip. So too the nature of the speech disability is influenced by the particular region of the cortex involved. Thus if the lesion is in the neighborhood of the lower part of the precentral and postcentral convolutions of the dominant hemisphere the speech defect tends to be of the *verbal* type. In injury to the temporal lobe the speech defect tends to be of the *syntactical* type. In a lesion in the region of the angular gyrus of the dominant hemisphere the patient has difficulty, particularly, in finding names for things (*nominal defect*); damage to the cortex in the region of the supramarginal gyrus results in a *semantic defect*.

ANARTHRIA OR DYSARTHRIA (LITERALLY NO ARTICULATION OR DIFFICULT ARTICULATION)

Anarthria or dysarthria is loss or difficulty of speech due to paresis, paralysis or ataxia of the muscles concerned in articulation. There is no impairment of the psychical aspects of speech, i.e., "internal speech" is unaffected; there is no difficulty in the comprehension

of spoken or written speech. Other functions, e.g., swallowing, which are dependent upon the same groups of muscles as those used in speech, are also frequently affected. The condition may result from a lesion in the internal capsule or corpus striatum, bulbar nuclei or peripheral fibers, or from disease of the muscles themselves. Since the muscular mechanism of speech is innervated from both sides of the brain unilateral lesions are not followed by permanent anarthria. A lesion of the cerebellum or of its connections may also cause disordered control of the muscles of articulation (p. 931).

APHONIA (WITHOUT VOICE)

In this condition the patient can whisper but he cannot speak aloud. The muscles of articulation, tongue, lips, etc., are unaffected. Aphonia is due to the loss of power in the adductors of the vocal cords and is seen in lesions of the laryngeal nerves, but most commonly as a result of laryngitis or of hysteria.

APRAXIA AND AGNOSIA

APRAXIA (UNABLE TO ACT)

This is the inability to perform purposeful movements at will either by command or in imitation, though the muscles concerned show no paralysis or ataxia, and the patient understands perfectly what is required of him. He may, for example, when asked to protrude his tongue, be unable to do so, yet a moment later may without thought lick his lips. The defect is evidently in the psychical sphere and not due to disease of the cells of the motor area or of the pyramidal fibers. It is thought to be due to the interruption of association tracts connecting the precentral gyrus with higher psychical regions of the cortex where impressions of the movements of muscles are received, synthesized and stored as kinesthetic memories. This higher ideational area probably lies in the region of the left supramarginal gyrus in right-handed persons. A lesion of this region may cause bilateral apraxia; one confined to the anterior part of the corpus callosum is likely to interrupt fibers passing from the left hemisphere to the right precentral convolution and so cause apraxia of the left side.

AGNOSIA (NOT KNOWING)

Agnosia is a defect in which familiar objects, persons and places fail to be recognized (*visual agnosia*) though sight is normal; or the meaning and significance of sounds are not appreciated (*auditory agnosia*) though hearing is unaffected. The subject of visual agnosia is unable to name an object, not that he is aphasic in the true sense, but simply because the object is quite strange to him. If he does not recognize a written word it is on account of his general imperception, and not a result of a specific defect in the language faculty. When shown an object and asked to use it he behaves quite differently from the apraxic patient who recog-

nizes it but is unable to perform the necessary movement. The agnostic executes the movement well but it is inappropriate. If given a toothbrush, for example he may attempt to light and smoke it, or if given a cigar may use it to brush his teeth. The patient suffering from auditory agnosia cannot appreciate music or carry out oral commands. If these are given in writing they may be well executed.

EPILEPSY

Epilepsy is a condition characterized by recurring attacks or "fits," which when exhibited in typical form, consist of abrupt loss of consciousness and generalized convulsions. Two stages of the attack or seizure are recognized. In the first or *tonic stage* the muscles contract tonically, the spasms often twisting the facial features and holding the head and limbs in distorted positions. The arms are most commonly flexed and the lower limbs rigidly extended. After a few seconds the tonic spasm gives place to jerking movements often violent, of the limbs, face and muscles of mastication. This is spoken of as the *clonic stage*. Either during this stage or in the tonic stage the tongue may be bitten. Before the onset of the convulsion a large proportion of epileptics receive a warning in the form of a sensation or hallucination, the character of which varies in individual cases. The warning sensation or *aura*, as it is most commonly called, may be auditory, e.g., voices, music, etc., visual, e.g., flashes of light, sparks, etc., olfactory, gustatory, cutaneous, visceral, or kinesthetic, i.e., a sensation of movement of some part of the body. The kinesthetic sensation may be accompanied by actual movement of the part. Turning of the head and trunk to one side and deviation of the eyes are commonly observed. The patient sometimes utters a cry or scream—the epileptic cry—just before consciousness is lost. Loss of consciousness, however, does not always occur. On the other hand, attacks of sudden loss of consciousness, usually of brief duration, may occur without convulsions; such minor seizures are referred to as *petit mal* to distinguish them from the major attack or *grand mal*. After the convulsion the subject remains for a time in a stupor and may, especially after milder attacks, perform automatic acts, of which he has no recollection after regaining consciousness. This *automatism* occurs also in attacks of *petit mal*. Most commonly it consists merely in resuming some act or other upon which the subject was engaged before the onset of the seizure. Sometimes a number of convulsive seizures occur in rapid succession, the patient fa-

ing to regain consciousness in the intervals between them. This very serious condition is called the *status epilepticus*.

PATHOGENESIS

(a) *Jacksonian epilepsy*

In this type the seizure is due directly to a gross lesion localized in some part of the cerebral cortex. For example, a tumor, a foreign body, a cerebral birth injury or a depressed fracture of the skull may, by stimulating the cortical tissue in its neighborhood, precipitate the epileptic fit. A seizure arising from a definite cause of this nature is spoken of as Jacksonian epilepsy after Hughlings Jackson, the English neurologist of the last century who first described it. The term *focal epilepsy* is also sometimes employed. The fit commences in the region of the body governed by the irritated area of the cortex, but soon spreads to involve other muscular masses. All of one side of the body or even the opposite side may ultimately become convulsed. In the "march" of the convulsion the order in which the different muscles are involved can frequently be seen to correspond to that of their cortical representation. When the lesion is in the frontal, parietal, temporal or occipital lobes, and involves the adversive fields (p. 889), the attack is commonly ushered in by movements of the head and trunk and deviation of the eyes to the opposite side.

(b) *Idiopathic epilepsy*

Epilepsy which cannot be explained by the presence of any gross organic lesion of the brain is called idiopathic. Though many theories have been advanced, the cause of this type of the disease remains obscure. There is a tendency today to look upon epilepsy as a symptom, or rather a group of symptoms common to several rather than as a single primary pathological state. Convulsions, whose features are indistinguishable from those of the epileptic seizure, occur in a number of conditions. In animals convulsions may be produced by injections of absinthe or caffeine. Hypocalcemia (p. 702), hypoglycemia (p. 584), cerebral edema or anemia and other states are accompanied by generalized convulsions of an epileptiform character.

With regard to the neural mechanism through which the fits are produced; some authorities believe that the convulsions are the result of *increased excitability of the cortex* and therefore comparable in their mode of production to those of

the Jacksonian type, or to those produced by experimental stimulation of the cortex. Others view the convulsions as a *release phenomenon* due to the inhibition of cortical areas which normally exert a controlling influence upon lower motor centers. According to Pollock and Davis convulsions of either the tonic or clonic type are not necessarily due to cortical discharge since they can be induced (by means of certain drugs, e.g., picrotoxin) in decerebrate animals.

Nor is there any general agreement as to the nature of the underlying factor or factors responsible for the seizures. A change in the acid base balance toward the alkaline side, a disturbance of the water balance, defective oxygenation of the arterial blood, instability of the vasomotor system resulting in spasm of the cerebral vessels, and abnormalities of endocrine function have all had their advocates. Others believe that the primary pathogenic factor lies within the cortical tissue itself—an inherited inferiority of nervous structure resulting in instability of the higher cerebral centers. The defect, according to this view, is psychological in nature—essentially one of personality. This is the so-called *psychogenic theory* of Clark. According to some, organic changes in the brain are responsible. Changes in the brains of epileptics have been observed at operation and post mortem; destruction of cells and sclerosis of the hippocampus—Ammon's horn—have been described by several observers. It is more likely, however, that the changes described are the result rather than the primary cause of the seizures. They are found usually in inmates of institutions, i.e., subjects of the severer forms of the disease.

A few words with regard to some of the other possible pathogenic factors: Geyelin was the first to connect *alkalosis* with epilepsy. He observed that during periods of starvation the epileptic attacks were reduced in frequency and less severe. He attributed the beneficial result to the ketosis which occurs during fasting. A ketogenic diet, that is, one high in fat content and low in carbohydrate, was later advocated by Wilder and by Peterman in the treatment of epileptics. A considerable degree of success has been reported from the employment of this treatment.

There is evidence that the *water balance* is disturbed in epilepsy. There are water retention and increased volume of the cerebro-spinal fluid and apparently an increase in intracranial pressure. Increase in the quantity of supracortical cerebro-spinal fluid (frontal and parietal areas) and of the fluid in the subarachnoid spaces generally, can be

demonstrated by encephalography in subjects of epilepsy. Since the days of Hippocrates the moist brains of epileptics have been remarked upon. Water intoxication (p. 19) is well known to produce convulsive seizures and the intravenous injection of a hypotonic solution into animals increases their susceptibility to the action of convulsant poisons. Hypertonic solutions, on the other hand, lower the intracranial pressure and reduce the convulsive tendency. Cerebral edema, from whatever cause, is likely to result in convulsions. Though it is not suggested that a disturbance of the water balance is the primary cause of the epileptic seizure, it is believed, nevertheless, as a result of these several observations that water retention and the resulting rise in intracranial pressure are predisposing factors. The dehydration treatment of epilepsy is based upon this belief. The patient is maintained upon a fluid intake restricted to from 8 oz. to 12 oz. daily, and foods of high water content curtailed. According to Fay, one of the chief proponents of this method of treatment, the good effects resulting from a ketogenic diet are due not so much to the ketosis produced but to the reduction in the water content of the body, since less water is retained upon a diet of protein and fat than upon one rich in carbohydrate.

It is generally conceded that *defective oxygenation* of the arterial blood predisposes to convulsive seizures, and Lennox found that in a large proportion of the epileptics whom he examined between attacks, the oxygen saturation of the arterial blood was below the normal value. He also found that a seizure was readily induced in epileptic subjects by reducing the oxygen of the inspired air to around 10 per cent. Anemia of the cortex is also well known to be conducive to the production of convulsive seizures. Convulsions may be induced in the monkey by tying the carotids, and Stewart and associates found that in cats convulsions frequently occurred during the restoration of the blood flow to the brain after a period of complete arrest of the intracranial circulation. Also, the convulsions which occur in subjects of heart block (p. 192), or accompanying the depressor reflex resulting from stimulation of a hypersensitive carotid sinus (p. 245) are attributed to a temporary anemia of the brain.

During the epileptic attack pronounced *vascular changes* occur in the cortex. These have been observed during operations by Foerster, Penfield and other neurological surgeons. According to

Foerster, constriction of the pial vessels and pallor of the cortex occur during the tonic stage, vascular dilatation leading to marked congestion of the surface of the brain during the clonic stage. Constriction of the retinal vessels may also be observed during the attack. It is perhaps tempting to assume that the vascular constriction, and the resulting anemia of the cortex, is the cause of the fits and that the primary defect is some abnormality of the vascular nerves. From the evidence, however, such a conclusion is not justified; the vascular constriction may simply be an associated phenomenon—another manifestation of the underlying pathological state. Penfield, from his observations of the exposed brains of a number of conscious epileptics, states that the one invariable vascular accompaniment of the epileptic seizure is constriction and cessation of visible pulsation of the pial arteries. Frequently the radial pulse also disappears. Pallor of the cortex—capillary constriction—though it was observed by Penfield upon some occasions during the attack, occurred more commonly after the attack was over. Though, occasionally, very definite improvement has resulted from removal of the cervical sympathetic, which furnishes constrictor fibers to the cerebral vessels, as a rule this operation is not followed by any appreciable benefit. Furthermore, experimental epilepsy can be readily induced in animals after cervical sympathectomy. These observations, however, do not necessarily exclude the possibility that spasm of the cerebral vessels plays a part in the epileptic attack, for removal of the sympathetic would not abolish the vascular reactions if, as Penfield believes, they may be brought about through local reflex arcs provided by nerve plexuses upon the intracranial vessels themselves.

A summary of the factors which may exert an influence upon epileptic seizures is given in table 80. The characteristics of the electro-encephalogram in epilepsy are described on page 906.

The study of convulsions produced experimentally in animals by various means, and of measures which raise the convulsive threshold (i.e., which reduce the susceptibility to convulsive seizures) has led to the discovery of a valuable drug for the treatment of the epileptic subject. In experiments on cats Merritt and Putnam found that the convulsive threshold to electrical stimulation of the cortex was raised most notably by *sodium diphenyl hydantoinate*, and have reported highly successful results from its clinical use.

HEADACHE

Headache is one of the commonest of symptoms, and occurs in a great variety of diseased states, e.g., arterial hypertension, chronic nephritis, gastrointestinal disease, etc., yet the mechanisms underlying its production are far from being clearly understood. It seems certain that the factors concerned are not the same in all instances. The headache occurring in such intracranial conditions as tumor, abscess or hemorrhage is usually the result of the general rise in intracranial pressure, but may also be due to the irritation of

TABLE 80

List of physiological changes in the brain which may influence seizures

(After Lennox and Cobb)

	CONDITIONS WHICH MAY TEND TO	
	Prevent seizures	Precipitate seizures
Oxygen	Rich supply	Poor supply
Acid-base equilibrium	Acidosis by means of fast-ing, fat diet	
	Ingestion of acids or acid-forming salts	Alkalosis by means of ingestion of alkali
	Breathing high CO ₂	Hyperpnea—"blowing off" CO ₂
Chemical constituents	Low chloride (?)	High chloride (?)
	High calcium (tetany)	Low calcium (tetany)
Water balance	Dehydration	Hypoglycemia Edema
Intracranial pressure	Decreased	Increased
Intracranial circulation	Impaired	Unimpaired

sensitive nerve endings in the immediate neighborhood of the lesion. As pointed out by Elsberg, sudden changes in intraventricular pressure, whether a rise or a fall, are likely to cause headache, quite apart from any significant change in general intracranial pressure. Severe headache lasting many hours frequently follows the withdrawal of cerebrospinal fluid by lumbar puncture. Elsberg considers that in these instances lowered pressure within the third ventricle, and upon the optic thalami, which form the ventricular walls, is the essential factor. For example, if a block exists in the ventricular system behind the third

ventricle, headache does not result from lumbar puncture. Headache also occurs during encephalography when the injected air enters the third and lateral ventricles. The site of the headache bears a relation to the location of the injected air, varying with different positions of the head.

Headache may result from neuralgia of the nerves of the scalp, from disease of the frontal sinuses, or from osteitis or periostitis of the cranium (syphilis, Paget's disease, etc.); or it may be a radiated pain from the extracranial branches of the trigeminal to its intracranial terminals. It may sometimes be due to pain (p. 860) referred from a thoracic or abdominal viscus to the superficial tissues of the head supplied by the trigeminal, which is related segmentally to the vagus. The temporary but severe pain felt in the frontal region by a normal person after quickly swallowing ice-cream is an example of a referred pain². It is not within the scope of this work to enter into a discussion of headache from the clinical viewpoint,³ but the possible factors concerned in the production of pain in the ordinary common headache and in migraine will be considered.

In healthy persons the most common causes of headache are eyestrain and constipation. The pain in the ordinary type of headache, and also in most other types is of intracranial origin. The sensitive regions are the vessels of the pia mater and their immediate surroundings, and the larger vessels of the dura mater. From observations upon conscious patients during intracranial operations it seems established that the cortical gray matter and the dura mater itself are insensitive. Fibers mediating pain are distributed in the intracranial branches of the trigeminal nerve. The latter, however, are not the only pathway for pain impulses from within the cranium for, according to Elsberg and Southerland, headache occurs after section of the sensory root of the trigeminal nerve on both sides; intracranial branches of the vagus probably contain pain fibers.

The sensitivity of the pial and dural vessels has led to the belief that the majority of headaches are of vascular origin, the pain being due to vasodilatation and the excitation of the sensitive nerve endings situated upon the vessel wall or in its immediate neighborhood. It is thought that vasoconstriction first occurs, followed by vasodilatation and congestion of the pia mater. The

³ For the more clinical aspects of the subject the reader is referred to an article by Spriggs (Lancet, 1935, 2, 1).

initial vasoconstriction and the resulting local anemia may also, it has been suggested, result in edema and a rise in intracranial pressure. The severe though brief headache which follows the intravenous injection of histamine—a potent vasodilator substance—can be cited in support of the vascular theory. In some persons who are subject to headaches, a headache with features identical with those from which the subject suffers is caused by the administration of histamine. In view of the discovery that the intracranial vessels are under nervous control, the production of headache through reflex action initiated from various parts of the body, and in excitement or emotional states, is readily understood upon the basis of a vascular mechanism. It is also reasonable to assume that certain toxic substances may, in some instances, induce headache through a direct action upon the vessels. The headache associated with constipation is, however, apparently of reflex rather than of toxic origin. It is often relieved very quickly by a movement of the bowels, a fact, as pointed out by Alvarez, which seems to preclude the possibility that it is the result of the absorption of toxins from the intestine (p. 509). In the headache accompanying visual defects, reflex vasomotor changes within the cranium and pain referred from the eye to the terminals of the trigeminal nerve, are probably the chief causative factors.

Not only the vessels of the meninges, but the intracerebral vessels and the choroid plexus as well, are supplied with nerve fibers, and the fact, as mentioned above, that headache follows the injection of air into the ventricles, indicates that the deeper parts of the brain are sensitive. It is possible, therefore, that vasomotor reactions involving the intracerebral vessels or variations in pressure within the ventricular system may be factors in the production of ordinary headache.

MIGRAINE. (Synonyms, megrim; hemicrania; sick headache.) This is a type of headache whose special features entitle it to be placed in a class by itself. The headache is periodic, severe and often accompanied by nausea and vomiting. In many instances some type of sensory disturbance (aura) ushers in the attack. This frequently takes the form of scintillating colored lights or the so-called fortification figures, that is, zig-zag luminous bands which are suggestive of the walls of a turret. The visual hallucinations have a homonymous distribution, that is, they occur in the right or the left halves of the visual fields (p. 1006). Temporary hemianopia may follow, or blindness of the

central part of the retina may accompany the visual sensations, which are then toward the periphery of the field of vision. Cutaneous, auditory or gustatory auras occasionally occur. The headache is localized at first but soon spreads to involve the entire half of the head; the pain is then on the side opposite to that of the hallucinations. Not unusually, however, the headache is bilateral, or is unilateral to start with, and later spreads to involve the opposite side of the head.

The mechanism underlying the production of migraine is a matter for speculation. The premonitory sensory phenomena quite clearly point to a cortical disturbance and strongly suggest that the condition has a vascular basis. According to Bramwell, the aura is associated with spasm of the pial vessels, the headache with vasodilatation, and, possibly, with localized edema. The pallor of the face which frequently accompanies the attack, and the constriction of the retinal and temporal vessels, also support the conception that migraine is of vascular origin. Migraine in some instances appears to be a form of allergy, like asthma (p. 366) and hay fever. It is conceivable, as Spriggs suggests, that an antigen of some sort (possibly taken in the food) combines with antibodies in the endothelial cells of the vessel walls and causes the liberation of histamine with consequent vasodilatation and localized edema—that is, an “intracranial urticaria.” This would result in pressure upon the sensitive nerve endings in the pia mater.

Several other theories have been advanced in attempts to explain the pain of migraine, e.g. increased pressure within the ventricular system due to temporary blockage of the foramen of Monro, or to hypersecretion by the choroid plexus. There is no evidence, however, that temporary changes of this character ever take place. Pool and his associates did not find the cerebrospinal fluid pressure greater in patients during the migrainous attack than in a group of normal controls. Timme subscribes to the theory that the headache, in certain instances at any rate, is due to swelling of the pituitary body within an abnormally small pituitary recess. This mechanical conception has not, however, received support from other observers who have been unable to demonstrate by roentgenography that the pituitary recess is significantly smaller in subjects of migraine than in those who have never suffered from an attack. Others hold the view that a low blood sugar is, in some cases, at least, an important factor, citing in support of their belief the headache of fasting and of hyper-

nsulinism, and the relief which follows the administration of glucose or of adrenaline.

There is some evidence that hypersecretion of the gonadotropic hormone (or hormones) of the pituitary may be a factor in the onset of the migrainous attack. Riley, Brickner and Kurzrok have reported that in twenty out of a series of twenty-nine female subjects of migraine the gonadotropic principle appeared in the urine preceding the attack. At the same time the female sex hormone (oestrin) was either absent from the urine or present in very reduced amounts. Of the two male subjects studied, one showed a similar relationship between the appearance of the pituitary principle in the urine and the onset of the attack; in the other subject an excretion of the pituitary principle occurred prior to four out of eight of his attacks. In support of the view that a disturbance in the gonad-hypophyseal mechanism plays an important rôle in the production of migraine these authors call attention to the following observations. The first attack of migraine frequently coincides with puberty; attacks commonly occur before menstruation, when the excretion of estrin is reduced and the gonadotropic principle may appear in the urine; the subject is usually free from attacks during pregnancy when the excretion of the estrogenic hormone is increased, whereas the gonadotropic (follicle-stimulating) principle of the pituitary is reduced; relief from the condition commonly follows the conclusion of the menopause, and in the case of men the attacks cease or become infrequent after the fifth or sixth decade.

Among the many agents which have been employed in the treatment of migraine are the following; sedatives such as *bromides*, *peptone* or *foreign protein injections*, *ergotamine tartrate* and the *estrone*. The latter, it will be recalled, depresses the gonadotropic activity of the pituitary, a fact which in the light of the views held by Riley and his associates, may explain the benefit which has been reported to follow its use. Estrone is especially effective in the treatment of headache associated with the menstrual period. The mode of action of ergotamine in relieving the headache is not clearly understood. Pool did not observe any consistent effect of the drug upon the pial or cerebral vessels. The dural vessels, however, are constricted by ergotamine; if, as some claim, the pain of migraine originates in the dural arteries the constrictor effect of the drug upon these vessels may explain the relief which follows its use. Ergotamine causes a rise in systemic blood pressure, an

increase in cerebral blood flow and a rise in cerebrospinal fluid pressure, effects which in no way explain its beneficial action.

The electro-encephalogram

In 1929 Berger discovered that changes in electrical potential could be recorded from the head of the human subject by means of pad electrodes applied to the scalp or needle electrodes placed in contact with the periosteum of the skull. In normal subjects three wave frequencies may be recorded—the *alpha*, *beta* and *delta* rhythms.⁴ The alpha rhythm consists of rhythmical oscillations in electrical potential occurring at the rate of 10 per second (fig. 379). The waves have a voltage of about 50 microvolts on the average. The alpha waves appear with the eyes shut but are abolished by visual activity or by mental effort (e.g., mental arithmetic); they return again as soon as the men-

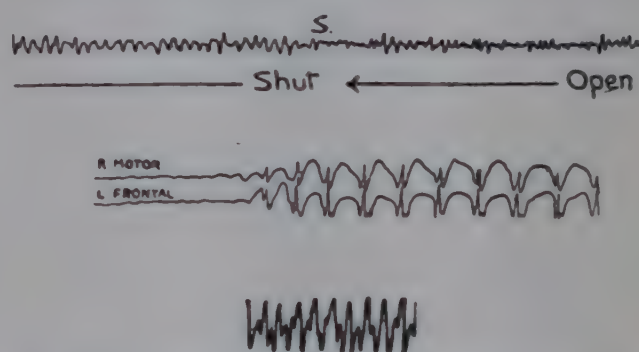


FIG. 379. Normal alpha rhythm, upper, *shut* and *open* refer to eyes (after Lemere); center electro-encephalograms during an attack of petit mal (after Gibbs and associates); lower, during a grand mal seizure.

tal work ceases. Adrian and Mathews found that the waves are present when the eyes are open, provided that the visual field is uniform (i.e., free from pattern). Any attempt of the subject to fix the eyes upon any detail results in the disappearance of the waves. A visual field which flickers causes the potential waves to assume a rhythm of the same rate as the flicker. Adrian and Mathews conclude that the waves are due to a spontaneous beat of an area of the occipital cortex concerned with pattern vision; when the cells of this area are not engaged in visual activities they tend spontaneously to discharge impulses at a fixed rate. The beta rhythm is faster than the alpha (25–50 per second) and of lower voltage (5–10 microvolts) and is obtained best over the precentral (motor) region of the cortex. The delta waves have a frequency of from 1 to 5 per second and a voltage of from 20 to 200 microvolts; they can be recorded very rarely

⁴ A faster rhythm (*gamma*) appears in rare instances.

from a normal adult while awake, but appear normally during sleep or during the waking hours in early childhood. Generally speaking, their presence in an adult, except during sleep, indicates some pathological process in the brain—tumor, epilepsy, raised intracranial pressure, mental deficiency or depression of consciousness by toxic or other factors. When present they tend to displace the alpha rhythm. Neither the beta nor the delta waves are abolished by closing the eyes. The electrical potentials just described are of cortical origin; the record of such changes might therefore be appropriately termed cortical electrograms. According to Kornmüller, records from different cortical areas show characteristic differences in wave pattern which change rather abruptly as the boundary between two areas of dissimilar histological structure is crossed.

Abnormalities of the electro-encephalogram in brain tumor, especially of so-called silent areas of the brain, and in epilepsy, promise to be of definite diagnostic value. In cerebral tumor or brain abscess, as shown by Walter and by Case, the functionally depressed brain tissue surrounding the lesion gives out waves of slow rhythm (delta waves) which, combined with a loss or diminution in the alpha rhythm over the occipital region may be of considerable aid in localization.

Epileptic seizures are characterized by pronounced departures from the normal rhythm. In *petit mal* attacks, large slow waves appear about a second before the attack is clinically manifest, and displace the previous rhythm. Each large wave is followed by a sharp spike deflection (fig. 379). Early in a *grand mal* seizure, waves of relatively high frequency (10–30 per sec.) and of low voltage appear, but as the attack progresses these fast waves give place to slower and larger waves which continue into the stage of stupor following the seizure. Delta waves may be a prominent feature of the electro-encephalogram of epileptics between seizures.

In normal sleep the pattern of the electrical potentials recorded from the brain varies with the depth of unconsciousness. During light sleep, delta waves make their appearance while the alpha waves superimposed upon the slower rhythm of the latter persist. In deep sleep the alpha rhythm disappears being replaced by delta waves, or in some instances by a faster rhythm with a frequency of about 14 per second. During the light sleep before awakening the record shows only an odd slow wave. As consciousness returns the tracing consists of an intermittent alpha rhythm which becomes continuous upon waking.

CHAPTER LXX

CONDITIONED REFLEXES. SLEEP

Definitions

The ordinary reflex with which we are all familiar is an inherited characteristic of the species and is not dependent upon previous experience. Its pathways are established at birth. This type Pavlov terms an *inborn* or *unconditioned reflex*. For example, food placed in the mouth of a newborn puppy evokes a secretion of saliva. The reaction depends solely upon the stimulation of receptors (taste, touch, etc.) in the mouth. When, on the other hand, the young animal sees or smells a piece of meat for the *first* time no secretion of saliva results. Yet if an animal who has eaten meat on previous occasions sees or smells a morsel, profuse secretion of saliva occurs. This reaction, which depends upon previous experience, Pavlov has termed a *conditioned* or *acquired reflex*. Its pathways are not fully established at birth but are developed by training. Quite evidently the reaction of the older animal is the result of an association established in the past between the stimulus applied to the receptors of the mouth, and the appearance or smell of the food, i.e., a visual or olfactory stimulus. The former is called the *unconditioned*, the latter the *conditioned stimulus*. Not only the qualities of the food itself but changes in the environment extraneous to the food, if they occur in association with feeding, can serve as conditioned stimuli.

Conditioned reflexes may be either of an excitatory character, e.g., the secretion of saliva, or have an inhibitory action. The former are termed *positive* or *excitatory*, the latter *negative* or *inhibitory*.

POSITIVE OR EXCITATORY CONDITIONED REFLEXES

In the great majority of the experiments performed by Pavlov and his school the secretion of saliva was chosen as the indicator of the conditioned response. In order to follow the secretory reaction with precision the opening of the parotid submaxillary duct is transplanted to the cheek and chin, respectively. The saliva is collected by means of a special apparatus consisting of a funnel placed over the duct opening and leading into a system of tubes. The secretion is measured in drops by means of an electrical recorder. The animal is held in a stand by means of straps and

occupies a sound-proof chamber separate from that of the experimenter (fig. 380).

The reflex is established in the following way. While the animal is being fed (unconditioned stimulus) a stimulus, e.g., a flash of light, which is quite alien to the food itself (conditioned stimulus) is applied. After this association of the two stimuli has been repeated a number of times, the flash of light alone (i.e., food is withheld) evokes a secretion of saliva. This is called a *conditioned alimentary reflex*. Motor reactions, e.g., movements of the lips and jaws, snapping, whining or barking, and movements of the limbs, accompany the salivary secretion and constitute an integral part of the reflex. The number of repetitions of the experimental procedure, or "lessons," necessary to establish the reflex varies in different animals and in experiments of different types. Many types of conditioned stimulus (visual, auditory, olfactory and cutaneous) have been employed by Pavlov and his associates.¹ In establishing the reflex the conditioned stimulus must precede the unconditioned stimulus and, except in the case of secondary and trace reflexes, to be presently described, must overlap it for at least a brief period. If the conditioned stimulus *follows* the actual feeding it is quite ineffective, i.e., it will not evoke a reflex when subsequently applied alone. After the period of training, in order to demonstrate the conditioned response satisfactorily, the animal should be alert, not drowsy, and preferably hungry; furthermore it should not be distracted by some extraneous stimulus, e.g., a strange sound or light, which sets up unconditioned motor reflexes.

Other types of positive conditioned reflexes

CONDITIONED DEFENCE REFLEXES. Acid injected into an animal's mouth (unconditioned stimulus) causes a profuse secretion of saliva which washes the offending material away. A condi-

¹ Among these are the following,—the sound of a metronome, horn, bell, buzzer, tuning fork, organ pipe or of bubbling water; variously shaped objects, lights, figures or rotating discs; thermal, tactile and painful cutaneous stimuli; the odor of such chemicals as amyl acetate or vanillin. The cessation of a previously continuous stimulus, e.g., a buzzer; the rapid change in the intensity of a stimulus, or even the change in the rate of a rhythmical sound, e.g., a beating metronome, may serve as a conditioned stimulus (see also p. 911).

tioned reflex to acid is readily established by a series of trials in which a conditioned stimulus, e.g., a light, and the unconditioned stimulus (acid) are applied in combination. Or if an animal has been given a colored acid, the animal salivates when shown water of the same color. Also, if a painful stimulus is applied to the animal's paw (unconditioned stimulus) during some form of conditioned stimulation (e.g., sound of a buzzer) the motor reactions (e.g., drawing up the limb, turning the head towards the injured part, etc.) which follow the application of the combined stimuli occur, after a few trials, when the conditioned stimulus is employed alone. The painful stimulus may serve also as a conditioned stimulus for a salivary reflex; then, unless the painful stimulus is intense the usual defence reactions are suppressed, salivation alone

the mere sight of the syringe, or the approach of the attendant who had previously administered the drug; the injection of an inert fluid is particularly effective.

SECONDARY AND TERTIARY CONDITIONED REFLEXES. A second stimulus may be conditioned by linking it up with a conditioned stimulus already firmly established. A defence conditioned reflex, let it be supposed, has been established with an electric shock to the front paw as the unconditioned stimulus and a touch upon the hind paw as the conditioned stimulus. A second neutral stimulus (e.g., the sound of bubbling water) is now applied and withdrawn a few seconds before the application of the primary conditioned stimulus (touching the hind paw) but the unconditioned stimulus (electric shock) is omitted. If the two stimuli are associ-

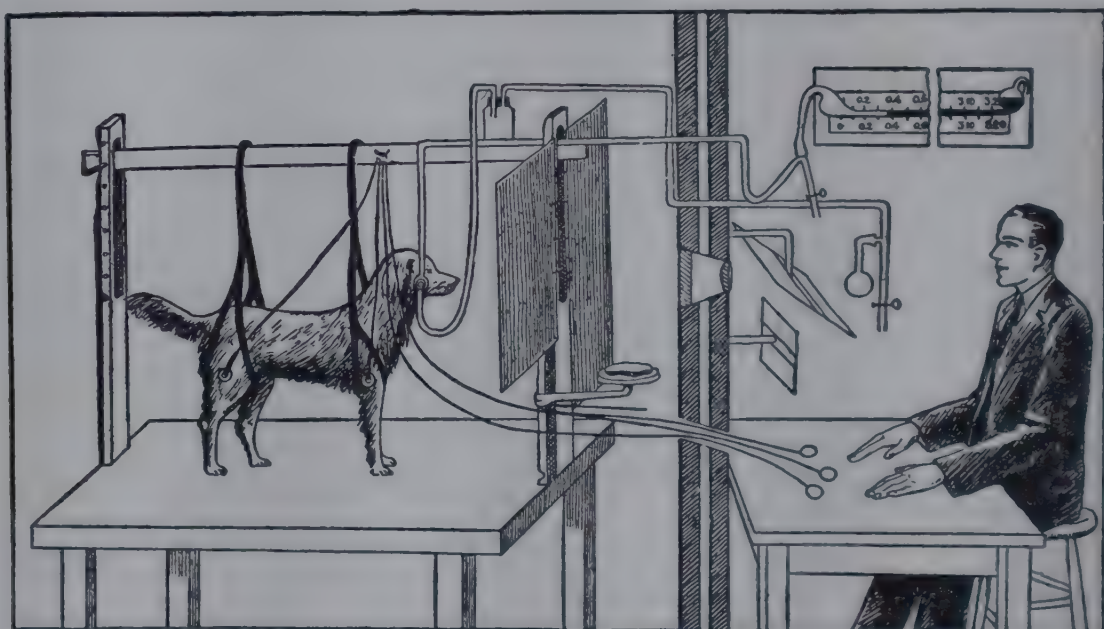


FIG. 380. Illustrating arrangements for experiments upon conditioned reflexes (from Pavlov, *Lectures on Conditioned Reflexes*, International Publishing Company, New York).

resulting when the stimulus is applied. The alimentary reflex is in this case stronger than the defence reflex. Pavlov points out that the subordination of the defence reaction by the alimentary reflex is seen when dogs are struggling among themselves for food. Minor injuries (e.g. of the skin) may then be sustained, but they do not evoke a reaction of defence; this is suppressed by the dominant food reflex. On the other hand, if the stimulus (such as one applied to bone) signals a more severe type of injury, or threatens the life of the animal, the defence reaction becomes prepotent.

Of great practical interest is the reflex which becomes established to the repeated injection of morphine. In the dog, morphine administration causes vomiting and salivation, followed by sleep. After a series of injections, these effects result from

ated in this way a number of times it is found that the second stimulus (sound of bubbling water) has itself acquired conditioned properties; when applied alone the defence reaction occurs. If a third stimulus (e.g., the sound of a tuning fork) is applied a short time before the second, but the primary conditioned and the unconditioned stimuli are omitted, it now, when employed alone, causes the conditioned response. It has not been found possible to establish a conditioned reflex of the fourth order, and conditioned reflexes beyond the second order cannot be established for alimentary conditioned reflexes.

TRACE CONDITIONED REFLEXES. In establishing this reflex the unconditioned stimulus is made to follow the conditioned stimulus after an interval when the reflex has been established the con-

conditioned response follows the conditioned stimulus after an interval of the same duration. For example, a tactile stimulus is applied to the skin for half a minute and then withdrawn; one minute later acid is injected into the mouth. After a number of repetitions it is found that when the tactile stimulus is applied alone, although no secretion occurs during its application, a response follows after a minute's interval. Also, if an animal is fed at regular intervals, say every 30 minutes, it is found that after a series of such feedings secretion occurs spontaneously, thereafter, at intervals of approximately 30 minutes, though no food is given. In these instances the time interval itself has evidently acquired the properties of a conditioned stimulus.

THE BIOLOGICAL SIGNIFICANCE OF CONDITIONED RESPONSES

Conditioned reflexes enter very largely into animal and human behavior. Many such reflexes are developed naturally as the experiences of everyday life become enriched, and associations accumulate. Stimuli arising in the environment are constantly calling forth conditioned responses of various types serving as signals to guide the animal in its choice of action. By training and discipline more complicated reflexes can be established, such as those forming the basis for the tricks of performing animals. In such instances the sound of a word (command) or a movement made by the trainer serves as a conditioned stimulus to some motor action of the animal. In the training and education of the child conditioned reflexes also play a prominent rôle. Animals with more highly developed nervous systems are capable of the more complicated reflexes, and though one can scarcely speak of certain conditioned reflexes, such as the secretion of saliva following the flash of a light or the sound of a tuning fork, as an intelligent act, the ability of an animal to develop conditioned responses is, nevertheless, a measure of its intelligence. Conditioned reflexes also play an important rôle in the psychology of sex and, according to Pavlov, in the induction of sleep (p. 918). Conditioned reflexes, which are established under the ordinary circumstances of life are termed *natural*. Those which are established experimentally or by special methods of training are called *artificial*. There is, however, no essential difference between the two.

INHIBITION OF CONDITIONED REFLEXES

Inhibition as applied to conditioned reflexes is divided by Pavlov into *external* or *indirect* and *internal* or *direct*.

A. EXTERNAL INHIBITION. The conditioned reflex is inhibited by some form of stimulation quite apart from the conditioned stimulus itself. The inhibition arises in a part of the brain other than that in which the conditioned reflex is initiated. For instance, some disturbing factor, a sudden noise, a strange smell, a light, a fresh object in the room, or the entrance of a stranger tends to abolish a conditioned reflex, which in quiet surroundings can be readily elicited. The extraneous stimulus arouses the animal's curiosity and distracts its attention or, in Pavlov's words, evokes an *investigatory reflex*. This purely unconditioned reflex consists of what its name implies—pricking of the ears and turning the eye and head toward the source of the distraction. If the extraneous stimulus is repeated often enough its inhibitory effect is weakened or abolished; the conditioned responses of an animal placed in strange surroundings are at first inhibited but return later. A painful stimulus also sets up an *unconditioned defence reflex*—barking, struggling and other motor reactions which exert an inhibitory effect upon the conditioned response.

B. INTERNAL INHIBITION. This will be considered under the following headings: (1) *extinction of the conditioned reflex*, (2) *conditioned inhibition*, (3) *inhibition of delay*, and (4) *differential inhibition*.

(1) *Extinction of the conditioned reflex*. If a conditioned reflex is repeated a number of times and the unconditioned stimulus (e.g., feeding in the case of an alimentary reflex) always omitted, the response becomes weaker with each repetition, its latent period lengthens progressively and the reflex finally disappears. The reflex is said to have undergone *extinction*. If, however, after every few repetitions of the reflex the conditioned stimulus is followed by the unconditioned stimulus, extinction does not occur. The former stimulus is then said to have been *reinforced* by the latter. For example, if a conditioned alimentary reflex has been established to the sound of a buzzer, the application of the latter alone calls forth at first a prompt and ample secretion of saliva. After a variable number of repetitions in which the conditioned stimulus is not followed by feeding, i.e., not reinforced, the secretion becomes less each time and finally ceases. After an hour or two the reflex recovers spontaneously. Extinction is due to inhibition of the cortical elements of the reflex. That it is not due simply to fatigue of the salivary gland or of the nervous centers is shown by the fact that after complete extinction, reinforcement of the conditioned stimu-

lus causes the reestablishment of the reflex. Moreover, the reflex continues at full strength after a great number of repetitions if it is followed every few times by reinforcement.

After a reflex has undergone extinction, some external stimulus may temporarily remove the inhibition. That is, just as an extraneous stimulus can inhibit the excitatory phase of a conditioned reflex, so also can it inhibit the inhibitory state. This is called *dis-inhibition* or the "*inhibition of inhibition*."

(2) *Conditioned inhibition*. If, after a positive conditioned reflex has been firmly established another stimulus is combined with the conditioned stimulus for a number of trials but reinforcement is always omitted, then, though the conditioned stimulus still causes the customary response when applied alone (and regularly reinforced), it is quite ineffective when in combination with the extra stimulus. For example, an alimentary conditioned stimulus is established to the beat of a metronome. Later, a buzzer is sounded with the metronome, but the combination is not followed by feeding. After a series of such trials the metronome causes a secretion, but the combined stimuli, metronome plus buzzer, are without effect. The sound of the buzzer is termed a *conditioned inhibitor*, and the inhibitory effect which it produces, a *negative* or *inhibitory conditioned reflex*. Usually, in order to demonstrate the inhibitory effect, the primary conditioned stimulus and the conditioned inhibitor must overlap. (It does not matter which commences first.) If one ends a second or two before the other commences, the inhibitory effect does not develop. Moreover, if the pause between the first and second stimulus is 10 seconds or so, the latter then causes a positive conditioned reflex of the second order (p. 908).

(3) *Inhibition of delay*. If during the establishment of a conditioned alimentary reflex, the conditioned stimulus is continued for only a brief period, 1 to 5 seconds, before the unconditioned stimulus is applied, then the conditioned response (secretion of saliva) follows almost immediately upon the commencement of the conditioned stimulus. That is, the reflex has a very short latent period. If after such a *simultaneous reflex* has been established, it is repeated day after day, but the conditioned stimulus is continued a little longer each time before the reflex is reinforced, the latent period becomes lengthened in proportion to the interval between the application of the two stimuli. The almost simultaneous reflex has been converted into a *delayed reflex*. In other words, postpone-

ment of reinforcement has caused the conditioned response to be inhibited during the first part of the action of the conditioned stimulus; during the latter part of the action of the conditioned stimulus the secretion of saliva commences and increases in amount up to the moment when reinforcement ordinarily would have occurred.

(4) *Differential inhibition*. This will be described in the next section.

The examples of internal inhibition just given show the high degree of discriminative and adaptive powers of which the cerebral cortex is capable. Though such adjustments are purely automatic they are effected with great delicacy and an apparent purpose. In the case of extinction, for instance the futility of secreting saliva for food which does not follow appears to have been "recognized." The purpose in conditioned inhibition is quite as evident as in positive conditioned reflexes and the inhibition of delay is clearly an adjustment which economically times the secretory response to the moment when food is "expected."

It is not only in these special instances that internal inhibition occurs, for all positive conditioned reflexes, though reinforced regularly, undergo inhibition if repeated over a period varying in different animals from weeks to months or even years. They become progressively weaker, the latent period lengthens out and they ultimately disappear. The tendency of conditioned reflexes to undergo inhibition is an inherent property. Reflexes in which the conditioned stimulus is of long duration, i.e. delayed reflexes, are more prone to disappear than those in which the unconditioned stimulus follows the commencement of the conditioned stimulus by a brief interval, i.e., simultaneous reflexes.

ANALYZING AND SYNTHESIZING FUNCTIONS OF THE CEREBRAL CORTEX

Of the numberless agencies in the environment to which the organism is exposed the great majority might be termed neutral in that they exert neither a beneficial nor an injurious effect. The actions of others are either of definite physiological value or detrimental to the animal's existence. Through the analyzing mechanism possessed by the nervous system the stimuli to which the latter types of agent give rise are given conditioned properties. Such stimuli are picked out to serve as signals for reactions on the part of the animal appropriate to the respective agents (beneficial or noxious); they are therefore of the utmost biological importance. The cerebral cortex also possesses synthesizing

mechanisms whereby individual stimuli are fused into conditioned complexes (p. 912).

The analyzers

Pavlov divides the neural mechanism of the organism upon which the discriminative faculties depend into a number of *nervous analyzers*. These are constituted of the nerves of special sense, and the afferent nerves of the joints and skeletal muscles, together with their respective receptors and central connections. Thus he speaks of *visual, auditory, olfactory, gustatory, cutaneous* and *motor analyzers*. The receptor of each class is especially responsive to its own type of stimulus—light, sound, etc. The central part of each analyzer, i.e., its terminations in the cerebral cortex, is capable of a very fine discrimination between the different intensities and qualities of stimuli within its own class. The visual analyzer, for example, discriminates between the intensity and quality of different visual stimuli, the auditory analyzer between the intensity, pitch and quality of sounds, the motor analyzer between the various messages (proprioceptive) received from the muscles and joints—and so on for the other analyzers.

In the past, the study of these analyzers, i.e., of the sense organs, has been based very largely upon subjective data gleaned from experiments upon the human subject. The discovery of conditioned reflexes, however, has provided a reliable method for the study of the analyzing functions which being purely objective can in consequence be employed in animal experimentation; the conditioned salivary secretion, for example, is a reaction which readily lends itself to precise measurement and timing.

Generalization and differentiation

If a conditioned reflex is established, say to the sound of a tuning fork of 800 cycles per second (c.p.s.), it is found that tones somewhat higher or lower in the scale have also acquired conditioned properties. Also, after a conditioned reflex has been established to a tactile stimulus applied to a certain definite skin area, the stimulation of neighboring areas is also effective. The response, however, becomes weaker the farther away from the original area that the stimulus is applied. This *generalization of stimuli*, as Pavlov calls the phenomenon, is seen also in the case of olfactory, visual and other analyzers. If, however, the original definite stimulus, for example the tone of 800 c.p.s., is always followed by reinforcement while other tones having a higher or lower frequency are em-

ployed without reinforcement, then only the tone of 800 c.p.s. evokes a response. The allied stimuli are said to have undergone *differentiation* from the primary stimulus. Pavlov ascribes the phenomenon to a form of internal inhibition—*differential inhibition*. He believes that originally the excitatory process in the cortical part of the analyzer is widespread, but through the antagonism offered by the internal inhibition set up by non-reinforcement of the allied stimuli, it becomes localized to only a minute cortical area corresponding to the receptors affected by the primary stimulus.

The degree to which differentiation between various types of stimulus can be developed is a measure of the analyzing ability of the cerebral hemispheres and is often amazing. The following examples are taken from Pavlov's monograph.

1. AUDITORY STIMULI

(a) *Differentiation of pitch*

Primary stimulus 800 c.p.s.

Differentiated stimulus 812 c.p.s.

(b) *Differentiation of rhythm*

Primary stimulus 120 beats per minute of a metronome

Differentiated stimulus 118 beats per minute of a metronome (Andreyev).

(c) *Differentiation of intensity.* The difference in the intensity of two sounds was so slight that it was detectable by the human ear only when one stimulus was followed immediately by the other. Differentiation was perfectly effected by the dog when the two stimuli were separated by an interval of 17 hours.

(d) *Differentiation of timbre and direction of sounds* was also demonstrated but the exact limits of differentiation were not determined.

2. VISUAL STIMULI

(a) *Differentiation of direction of movement or of the position of an object*

Primary stimulus. Clockwise rotation of a disc.

Differentiated stimulus. Anticlockwise rotation of the disc.

(b) *Differentiation of figures and shapes.* Some of the figures which were differentiated are shown in figure 381. A luminous circle thrown upon a screen was readily differentiated from a series of ellipses of the same luminosity; the series started with one having its axes in the ratio of 1:2; of the remainder each successive one approached a little nearer to the circular shape. Differentiation just failed when the ratio of the axes was 8:9.

(c) *Differentiation of luminosity.* Two shades of gray which to the human eye appeared

exactly the same, even when viewed simultaneously, were perfectly differentiated by the dog when an interval of a minute separated the primary from the differentiated stimulus.

- (d) *Differentiation of colors* failed in all but one animal investigated, and even it gave a doubtful result. Color vision in the dog is therefore either absent or very rudimentary.

3. **DIFFERENTIATION OF CUTANEOUS AND PROPRIOCEPTIVE STIMULI.** Differentiation was obtained for various types of tactile stimuli, e.g., contact with rough or smooth surfaces, pressure with blunt points arranged in different patterns, scratching with a small

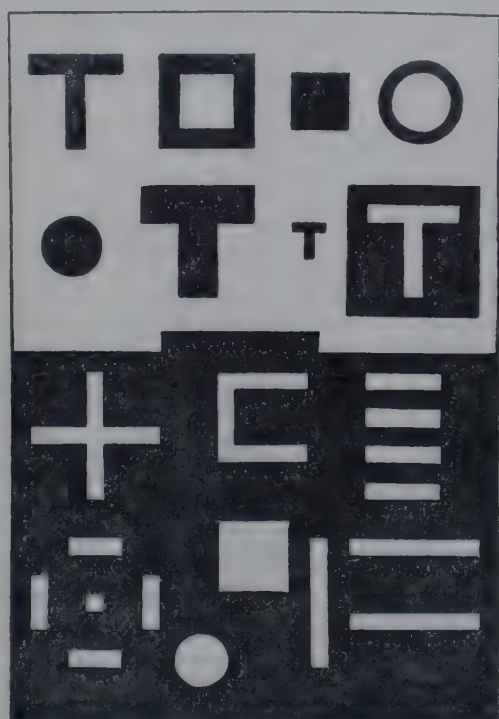


FIG. 381. Examples of different figures which were successfully differentiated in experiments upon a dog. The letter T, shown in the upper left-hand corner of the figure, served for the positive stimulus; the other black figures and the white letter T were differentiated from the positive stimulus. In another dog the white cross was the positive stimulus from which the other white figures were differentiated (from Pavlov, *Conditioned Reflexes*, Oxford University Press).

brush in different directions. Differentiation was also demonstrated between stimuli applied to different areas, for variations in temperature, and between various passive movements, e.g., flexion of ankle as against extension.

4. **DIFFERENTIATION OF OLFACTORY AND GUSTATORY STIMULI.** Corresponding differentiations were established for various odors (e.g., vanillin, amyl acetate, camphor, etc.) and for taste sensations e.g., meat powders, sugar, cheese, etc.

Conditioned vasomotor responses have been established in human subjects, the unconditioned response (vasoconstriction of the opposite hand) being induced by immersion of one hand in ice-cold water. Ringing of a bell, a light pattern or a word spoken aloud by the

experimenter and whispered by the subject were used as conditioned stimuli.

"Experimental neurosis." When an animal is presented with a problem which requires a fine degree of differentiating ability, i.e., when a conflict between inhibitory and excitatory processes is set up, either inhibition or excitation may gain the upper hand with the suppression of the opposite process. In the former event the animal may become drowsy and fall into a deep sleep (p. 919), whereas in the latter a nervous disturbance develops during which even gross differentiation cannot be accomplished. To give an example, a dog was required to discriminate between two visual stimuli, a circle and an oval, the former being followed by feeding (positive stimulus), while the latter was not reinforced (negative stimulus). Differentiation was made more and more difficult by making the oval at each successive trial more nearly circular. The experiment proceeded smoothly until the axes of the two figures had a ratio of 8:9. The animal then became fractious, howled and whined in its cage, struggled with its harness and became incapable of discriminating between any oval shape and a circle. Not until after a prolonged rest was the animal's power of discrimination between the two shapes restored, but upon being then confronted with the same problem the nervous disorder returned. *"Experimental neurosis,"* as this state was termed by Pavlov, has also been induced in sheep and pigs by Anderson and Liddell. In some instances the condition was permanent, and Gantt has reported such a state which has persisted for upwards of four years. The neurosis in this latter instance developed as a result of a conflict aroused in the differentiation of two auditory conditioned stimuli—two closely similar tones. These interesting observations upon experimental neuroses give an insight into brain physiology. They have important psychiatric implications and may give a lead in the interpretation of certain nervous conditions in the human subject (see p. 891.)

Synthesis of stimuli

The development of the conditioned response is, in itself, evidence of the synthesizing or associative ability of the cortex. Further evidence is afforded by experiments with compound stimuli, i.e., the fusion of separate individual stimuli, whether these act upon the same or upon different analyzers, into a conditioned complex.

As an example of simultaneous stimuli acting

upon the same analyzer,—an alimentary conditioned reflex was established to a chord of three tones of equal intensity but of 85,256 and 786 c.p.s., respectively. Later each tone when sounded separately caused a response. The responses to the different tones were approximately equal but weaker than that caused by the chord.

A conditioned reflex may be established to a compound stimulus made up of two stimuli acting *simultaneously* but upon different analyzers. If the component stimuli are then applied separately and without reinforcement, it is found that one of the pair is effective but not the other. For example, a conditioned reflex to acid was established to a compound stimulus consisting of the simultaneous application of a tactile stimulus and a thermal stimulus of 0°C. The tactile stimulus when applied alone was found to be about as effective as the compound stimulus, whereas the thermal stimulus was quite ineffective. The results of experiments in which the component stimuli of the compound stimulus were of unequal strengths, and applied to the same analyzer, indicate that the factor determining the effectiveness of the stimuli, when applied separately, is their relative intensity. The thermal stimulus used in the foregoing experiment may therefore be regarded as being the weaker of the two stimuli. Visual stimuli are also weaker than those acting upon the auditory analyzer. For example, after a conditioned reflex had been established to a compound stimulus made up of a tone and a light, the tone by itself caused a response, whereas the visual stimulus was quite ineffective. However, the weaker stimulus undoubtedly plays its part in the combination, for if the stronger component is applied repeatedly without reinforcement by the unconditioned stimulus, but the compound stimulus is constantly reinforced, the stronger stimulus by itself becomes ineffective, whereas the compound stimulus retains its full effect.

The cortex is also able to synthesize *successive* stimuli into a compound conditioned stimulus. For instance, a flash of light (L), a cutaneous stimulus (C) and the sound of bubbling water (S) when applied in the order (L—C—S) were compounded into a positive conditioned stimulus. The reverse order (S—C—L) after differentiation (by non-reinforcement) was entirely without effect.

Similarly, four tones having vibration frequencies of 290, 325, 370 and 413 c.p.s. respectively when sounded in this order (1, 2, 3, 4) were successfully differentiated by a dog from all other

sequences (e.g., 4, 3, 2, 1; 4, 3, 1, 2; 4, 1, 3, 2; 4, 2, 3, 1, etc., etc.).

The series of sounds in a word (e.g., a dog's name) or in a command is a familiar example of a successive compound conditioned stimulus.

Irradiation and concentration

These features are best illustrated by citing an actual experiment. The skin of the hind limb was stimulated at 5 separate places. One of these situated upon the paw was differentiated by non-reinforcement in the usual way from the other four. That is, the place upon the paw was given inhibitory properties (p. 911). The other four places, which through reinforcement were given positive conditioned properties, were placed at progressively further distances along the limb from the inhibitory place. It was found that if the latter was stimulated three times in succession, and one minute after the last stimulation, the positive place nearest the inhibitory place was then stimulated, there was complete failure of the usual conditioned response. Stimulation of the next (second) excitatory place one minute after the last application of the inhibitory stimulus was followed by a response half as great as usual. The remaining two places (third and fourth) gave a normal or somewhat greater than normal response (see positive induction, p. 914). When the number of the previous stimulations of the inhibitory place was increased, and the interval following the last one shortened to $\frac{1}{4}$ minute, all four excitatory places gave a reduced response. As time elapsed the furthest place was first freed from the inhibitory influence, and the others in the order of their positions from the inhibitory place. The point nearest to the latter in some cases did not give a full response until the lapse of 10 minutes after the application of the last stimulus to the inhibitory place. It can also be shown that if, by means of extinction, inhibitory properties are given to one of the four excitatory places the inhibitory process spreads to involve the others.

These results are taken to indicate that each stimulated area has its circumscribed representation in the cortex. Inhibition initiated in the cortical cells to which the inhibitory place is projected *irradiates* to involve the cortical projection areas of the positive places. The gradual release of the cortical areas from the inhibitory influence, and its retreat to the original cortical cells corresponding to the inhibitory place is called the *concentration of inhibition*. Irradiation and concentration are antagonistic processes. These

processes can also be shown for the acoustic analyzer and they most probably exist for other analyzers as well. The following is an illustration of irradiation within the acoustic analyzer. Positive conditioned reflexes were established respectively to the beat of a metronome, to a musical tone and to a buzzing sound. When the reflex to the buzzing sound or to the metronome was extinguished the inhibitory process spread to involve the reflex to the musical tone.

Irradiation is not confined to the analyzer in which the inhibitory process originates. It can be shown that the inhibitory process initiated in one analyzer spreads to others and may involve the entire cortex. For example, a positive alimentary conditioned reflex was established to a tone of 4000 c.p.s.; a note a semitone lower than this was given inhibitory properties by differentiation. When the inhibitory stimulus was applied a short time before a visual conditioned stimulus,

ties of a stimulus developed by means of differentiation can be readily destroyed again (disinhibited) by repeated reinforcement. If, however, application of the inhibitory stimulus is preceded by a positive one and both are reinforced the inhibitory properties of the former are strengthened and can be abolished only after a great number of trials. Thus, a metronome beating at a rate of 60 beats per minute served as a positive conditioned stimulus and a rate of 120 beats per minute as a differentiated (differential inhibition, p. 81). The inhibition was then almost abolished by reinforcement but was reestablished again when the differentiated stimulus (rate of 120 beats per minute) was preceded by the positive stimulus (rate of 60 beats per minute). The results are shown in table 81, given by Pavlov.

POSITIVE INDUCTION in its simplest form may be illustrated as follows. A positive conditioned reflex was established to stimulation of the foot of the hind paw. A stimulus to the hind paw was given inhibitory properties by differentiation. When the excitatory place (forepaw) was stimulated immediately after the application of the stimulus to the inhibitory place, the positive conditioned reflex was enhanced (salivary secretion increased by 50 per cent). The excitability of the cortical area receiving impulses from the forepaw had evidently been increased as a result of inhibition of the cortical area corresponding to the hind paw. The excitability of the cortex in proximity to the inhibited area is enhanced for the moment but then becomes depressed as a result of the irradiation of the inhibitory process. When dealing with irradiation it was pointed out that the inhibitory effect was demonstrable for several seconds after the application of the inhibitory stimulus. Pavlov holds the view that these two processes, positive induction and irradiation of inhibition (or negative induction and the irradiation of excitation), are constantly interacting with one another and spread wave-like over the cortex. Positive induction precedes, respectively negative induction, spread of the inhibitory or excitatory process.

THE EMPLOYMENT OF CONDITIONED REFLEXES IN THE STUDY OF CORTICAL FUNCTION. Information concerning the localization of functions in the cortex was obtained by, first, firmly establishing a conditioned reflex involving one or other analyzer, then excising a certain portion of the cortex and studying the effects of the operation on the conditioned response.

TABLE 81

TIME	CONDITIONED STIMULUS APPLIED DURING 30 SECONDS	SALIVARY SECRETION IN DOGS DURING 30 SECONDS
11.25 a.m.	60 beats	0
11.30 a.m.	60 beats	0
11.42 a.m.	60 beats	3
11.49 a.m.	60 beats	4
11.56 a.m.	120 beats	8½
12.06 p.m.	60 beats	0

All the stimuli were accompanied by reinforcement

the reflex which had been established to the latter, as well as that established for the positive auditory stimulus, (tone of 4000 c.p.s.) was inhibited.

Irradiation and concentration of excitation occur in a manner analogous to that described for inhibition. Generalization (p. 911) is ascribed to the irradiation of excitation from the primary cortical focus. Differential inhibition, on the other hand, antagonizes the excitory process and concentrates it within the original cortical area.

Induction

Induction is a feature of conditioned reflex action analogous to the phenomenon of the same name described as occurring in spinal reflexes (p. 813), namely, the increase of inhibition caused by a preceding state of excitation (*negative induction*) or an increase of excitation caused by a previous state of inhibition (*positive induction*). Induction is therefore a reciprocal process.

NEGATIVE INDUCTION. The inhibitory proper-

Removal of the entire cortex

The dog removal of the entire cortex results in complete and permanent loss of all conditioned responses, natural or artificial; new conditioned reflexes cannot be established. The decorticated animal responds to crude unconditioned stimuli, e.g., a bright light or sound, its responses being frequently those of resentment or rage (p. 884). The unconditioned salivary reflex is at first but eventually becomes stronger than normal.

Removal of a limited portion of the cortex

Removal of a limited portion of the cortex, e.g., temporal or occipital lobes, causes the disappearance for a time of all "artificial" conditioned reflexes, and sometimes of the "natural" ones as well. Unconditioned reflexes, which are dependent upon subcortical centers, remain in abeyance for a few hours or may not disappear at all. The recovery of conditioned reflexes depends upon analyzers, other than the one which has been directly injured, occurs after a few days, and is nearest to the excised area recovering later than those farther removed. The positive conditioned reflexes when they return are frequently of the normal strength. Inhibitory processes, on the other hand, much weaker than normal, take a longer time. Incomplete recovery of the injured cortex or eventually takes place. After scar tissue has formed convulsions frequently occur, being preceded by a complete disappearance of conditioned responses.

THE ACOUSTIC ANALYZER is centered in the temporal lobe. Extirpation of both temporal lobes is followed by a very temporary loss, if any, of auditory unconditioned reflexes (e.g., pricking the ears to sound). The auditory conditioned reflexes may not return for several weeks or months, and are never fully restored. The more discriminating reactions are particularly lost. Discrimination (p. 911) of the frequency, pitch and quality of sound is possible, but the powers for more complicated analyses and syntheses are not regained. The animal, for example, never answers to its name, and the discrimination of other types of compound auditory stimuli (p. 913), e.g., a descending from an ascending scale of tones, cannot be established.

An experiment upon the peripheral portion of the auditory analyzer may be mentioned here, since it has a bearing upon Helmholtz' theory of hearing. Destruction of the organ of Corti in the upper part of the cochlea (sensitive for lower tones) resulted in a loss of condi-

THE VISUAL ANALYZER is situated mainly but not exclusively in the occipital lobe. According to Pavlov the visual analyzer is probably spread over the entire cortex. Complete bilateral extirpation of the occipital lobes causes effects upon the visual conditioned reflexes corresponding to those upon the auditory reflexes which follow removal of the temporal lobes. Conditioned responses to changes in the intensity of illumination (e.g., switching on a high power lamp) established before operation returned upon the fifth day following the extirpation of the occipital lobes as well as of a considerable area of the cortex lying anterior to them. Differentiation was established between a luminous cross and a circle illuminated to the same intensity. It was found impossible, however, to establish conditioned reflexes to specific objects. The explanation for this probably is that the appearance of an object changes with the illumination, with its distance from the eye and the angle from which it is observed. Its recognition under different conditions of lighting, position, etc., therefore requires a much greater power of analysis and synthesis than that required for the differentiation of a flat luminous shape. The animal deprived of its occipital lobes is able, nevertheless, to avoid objects placed in its path. They are detected simply by the changes in illumination (lights and shadows) which their presence creates.

The findings described above, namely, that complete decortication in the dog abolishes all conditioned reflexes, and that removal of the temporal or occipital lobes impairs, respectively, auditory, and visual conditioned reflexes, but does not destroy them permanently and completely, lead to the following conclusions concerning the functions of the cortex, so far at any rate as the auditory and visual senses are concerned. (a) Though rudimentary reactions can be carried out through subcortical connections, the processes underlying conditioned reflexes are dependent upon the activity of the cerebral cortex. (b) The highest powers of analysis and synthesis are localized to definite areas, each of which may be regarded as the "nucleus" of a given analyzer. (c) The analyzer, however, is not rigidly confined to this area but extends into other cortical regions in which less complicated types of analysis can be

tioned reflexes which had been established to tones of the lower part of the musical scale (frequencies lower than 600 d.v. per minute). Reflexes to higher tones were unaffected.

undertaken. Experiments involving other analysers have yielded evidence pointing in the same direction:

These results of cortical extirpation cannot be directly applied to the human subject since the functions of subcortical centers of hearing, sight, etc., in lower animals have not, as in man, been entirely usurped by the cortex. Nevertheless, Pavlov's observations are, broadly speaking, in harmony with modern conceptions of cortical functions (see p. 891). A given sensory function, though primarily "centered" in a certain cortical area, is dependent for its full development upon other areas as well.

THE EFFECTS OF DRUGS UPON CONDITIONED REFLEXES

Caffeine and *strychnine* increase the effects of positive conditioned stimuli and weaken internal inhibition. After a dose of less than 1 grain (0.025 to 0.05 gram) of the former drug, extinction (inhibition) of a conditioned reflex is effected with the greatest difficulty. *Bromides* act by strengthening internal inhibition, and not by directly depressing excitatory processes; under their influence the extinction of positive conditioned reflexes is facilitated. *Alcohol* in moderate doses weakens internal inhibition. Recently Andreyev and Pugsley have found that the *hypercalcaemia* resulting from parathormone or ergosterol overdosage causes an exaggeration of inhibitory processes, the after effect of inhibitory stimuli is enhanced and extinction of positive conditioned reflexes accelerated. The inhibitory effect of the hypercalcaemia is antagonized by caffeine.

THE PHYSIOLOGY OF SLEEP

THE DEPTH OF SLEEP

The depth of sleep is not constant throughout the sleeping period but varies from hour to hour. Experiments upon man in which auditory stimuli were employed to arouse the subject at different times, or the movements of the sleeper were recorded (the depth of sleep being assumed to be inversely related to the amount of muscular movement) indicate that the depth of sleep follows a characteristic curve. In most adults sleep deepens rapidly to the end of the first hour, after which it lessens sharply for a time, and then more slowly till the time of waking. In children the sleep curve shows two maxima, i.e., two periods of the deepest sleep, one of these is reached in the first or second hour, the other between the eighth and ninth hours; the curve then falls rapidly to the time of waking. Generally speaking, sleep taken

during the daytime is lighter than that at night. Deep sleep is dreamless, dreamless only during light sleep and chiefly in the which just precedes waking. In sleep consciousness is not uniform for all senses, that of sleep is greatest for the sensations and least for those of pain, hearing and

The sleep requirement of different persons widely; it also varies with age. The following average figures for the amount of sleep at different periods of life.

New-born infant	18
Growing children	12
Adults	8
Old persons	5

PHYSIOLOGICAL CHANGES ACCOMPANYING

During sleep most bodily functions are to their basal levels. The blood pressure is the systolic pressure showing a decline of to 30 mm.Hg. The lowest level is reached the fourth hour of sleep; this level is maintained until a short time before awakening, after which pressure commences to rise again. Maschke found that if the sleep was disturbed by dreams the blood pressure might be well above the normal waking level, e.g. 130 mm.Hg., up to 180 or even 200 mm.Hg. pulse rate is slowed by from 10 to 30 beats per minute, the metabolic rate is reduced by from 10 to 15% below the basal level and the rectal temperature by a fraction of a degree Fahrenheit. The regulating mechanisms are depressed: respirations are slowed as a rule, and also become more costal in character; they also become irregular or periodic. Muscular activity is minimal, the knee jerk is abolished, and Babinski may be present. The three most somatic reflexes are definitely raised: motor reflexes, however, are more or less present. In most animals the righting reflexes are retained. The pupils are usually constricted; the reflex is retained. The eyeballs are turned inward and outward. Urine volume is reduced, absolute excretion of urinary phosphate is increased, and the specific gravity ratio of the sweat glands is not increased; according to Hartnagel the amount of fluid lost per hour in sleep is nearly equal to that lost during a corresponding period of muscular exercise. Gastric secretion is or little altered during sleep. The con-

stomach continue and may be more usual; the rate of digestion is about normal during the waking state. *Lacrymal* secretions are reduced.

of interest to give an account of the nervous system of prolonged

In Kleitman's human experiments were kept awake for periods ranging 14 hours. The knee jerk remained at disappeared promptly when the to sleep at the termination of the annia, and a positive Babinski was. The latter was attributed to the of a block in the corticospinal path- pupillary response remained brisk the wakeful period. There seemed to firmment of the mental processes, and to auditory and visual stimuli were usual. The threshold for pain stimuli lowered, whereas that for touch d. The power to maintain equi- dged by the ability to stand with the was grossly impaired. This defect d to neuromuscular fatigue and the duction in muscle tone, rather than ment of labyrinthine function itself. of wakefulness which would be lethal n subject is not definitely known. after being kept awake continuously though they may survive for much s. Young animals are much more o loss of sleep than older ones. he nerve cells of the cortex, e.g., and shrinkage of the cell bodies, scribed as resulting from prolonged forced wakefulness in animals.

THEORIES OF SLEEP

and nature of sleep have aroused om the time of the Greek philosophers t day, but though hypotheses are ten ill-founded, facts which might upon the underlying processes are alt to obtain. A discussion of only more important theories, will be

THEORY (Lépine, Duval). This theory e demonstration by Cajal that there omical continuity between adjacent erely points of contact, for which the was later suggested by Foster. The ostulated that the function of the cells rtical centers was suspended as a result

of the retraction of the dendritic processes, and the consequent break in contact between neurones. Though some histological evidence was cited in support of this conception, the theory was mainly speculative.

(2) CEREBRAL ISCHEMIA THEORY. Howell suggested that fatigue of the vasomotor center with consequent vasodilatation of the peripheral vessels, especially of the skin, and reduction in cerebral blood flow was the primary change responsible for the onset of sleep. The flushed skin of the sleeping subject, the fall in blood pressure and the well-known feeling of drowsiness following a meal (which presumably was the result of the diversion of blood to the splanchnic area) lent plausibility to the theory. From ancient times the carotid artery (Karoō = I sleep) has been believed to be connected in some way with the mechanism of sleep, for it was recognized that compression of this vessel was not uncommonly followed by unconsciousness. In later times the loss of consciousness following pressure upon the neck was attributed to vagal stimulation, with consequent inhibition of the heart and a reduction in intracranial blood flow. We know now that the unconsciousness is due to the fall in blood pressure brought about through the carotid sinus mechanism.

The unconscious states caused by a reduction in cerebral blood flow are not, however, akin to normal sleep. Vulpian observed some years ago that, though stimulation of the cervical sympathetic in animals caused cerebral ischemia, sleep was not induced. Moreover, Gibbs has recently shown by means of an electrically heated stylet inserted into the jugular vein of human subjects (p. 291) that no diminution in blood flow through the brain occurs during natural sleep. It is possible, nevertheless, that there may occur a reduction in the blood supply to a limited area of the brain whose activity is essential for the waking state. A limited vascular change of this nature might not be revealed by observations upon the total intracranial blood flow. With regard to the carotid sinus and its possible relationship to the sleep mechanism, a recent interesting observation should be mentioned. Weiss and his associates describe states resembling normal sleep as resulting from pressure upon the sinus in certain susceptible subjects. The notable feature of this reaction is that unconsciousness is not accompanied by a significant change in heart rate, blood pressure or in the blood flow through the brain. In some instances there was actually a rise in blood pressure preceding and during the unconscious state. The

effect of carotid sinus stimulation in these instances appears to have a purely nervous basis, the sensory part of the mechanism being the sinus nerve and the receptors in the sinus wall. The brain center or centers involved are unknown. Koch also reported in 1932 that in dogs recovering from anesthesia, stimulation of the carotid sinus caused the immediate cessation of muscular movement, the head and tail of the animal gradually hung more and more limply, or as Koch expresses it, "The animal sinks loosely together, often on its side, to be as in sleep."

(3) **CHEMICAL THEORIES.** Several chemical theories of sleep have been proposed. One of the earliest of these was that fatigue products, especially lactic acid, formed in the tissues generally, acted by depressing the function of the cortex. Against this view is the well-known fact that one need not be fatigued in order to sleep; on the other hand, a person may be unable to sleep though utterly fatigued. Furthermore, the brain tissue actually derives energy from the oxidation of lactic acid.

A more recent chemical theory is that of Pieron. This observer claims that a substance, which he terms *hypnotoxin*, is produced by the brain tissue and acts as a soporific. He claims that the cerebrospinal fluid of a dog killed during sleep induces sleep when injected into another animal. Kroll makes similar claims, stating that an acetone extract of the brain of a sleeping or hibernating animal will cause sleep when injected into another. Holmes has been unable to confirm Kroll's findings. An extract prepared by Kroll's method either from sleeping or waking animals was found to be lethal through its toxic effect upon the heart. Ivy and Schnedorf have repeated Pieron's experiments and confirmed his observation. They found that the injection of cerebrospinal fluid of a dog kept awake for several days induced a state of depression resembling deep sleep in rested dogs, when introduced into the cisterna magna or cerebral ventricle. The effect, however, is probably due, not to the presence of a sleep-inducing substance in the "fatigued" cerebrospinal fluid, but to a rise in intracranial pressure, since the injection of cerebrospinal fluid from rested dogs had a depressing action not considerably less than that of the "fatigued" fluid. No evidence in support of the theory (Dikshit) that *acetylcholine* liberation by the brain tissue is a factor in sleep was secured by these observers.

Zondek and Bier have advanced an interesting theory in which the pituitary plays a leading rôle. They state that the pituitary during the waking state has a higher concentration in bromine than any other tissue but that during sleep the bromide concentration of the gland diminishes while that of the medulla increases. These observers therefore believe that sleep is induced through the liberation of a bromine

compound from the hypophysis. They have named this substance *bromhormone*. The evidence upon which this theory is based is far from convincing.

(4) **THE HYPOTHALAMUS AND SLEEP.** Several observations both clinical and experimental point to the existence of a sleep center in the diencephalon. Hypersomnolence is a frequent accompaniment of tumors of the structures in the floor and walls of the third ventricle, or of inflammatory lesions involving the hypothalamic region. Hess claims to be able to cause sleep in animals by mild electrical stimulation of the diencephalon towards the anterior end of the cerebral aqueduct. He has also reported that ergotamine injected directly into the third ventricle induces sleep. Ergotamine paralyzes the motor and secretory fibers of the sympathetic. Since the parasympathetic and sympathetic centers are apparently situated in the hypothalamus, Hess argued that the drug by suspending the activity of the sympathetic center caused a preponderance of parasympathetic effects. Sleep, he concluded, was a parasympathetic function. He also draws support for his theory from certain manifestations of parasympathetic activity, namely, the pupillary constriction, bradycardia and vasodilatation which accompany sleep. Though this observer's idea that sleep is a parasympathetic function requires further experimental support before it can be accepted, the evidence for the participation of the hypothalamus in the sleep mechanism is very strong. Yet, contrary to the idea that sleep is caused by excitation of some part of the hypothalamus, other investigators believe that it results from the *depression* of hypothalamic activity. The hypothalamus is thus regarded as containing a waking center, sleep following its inhibition. Ranson and his associates, for example, have reported that sleep can be readily induced in cats by lesions confined to the mammillary bodies, but that it did not result from the stimulation of any part of the hypothalamus. Harrison also found that electrical stimulation of the hypothalamus caused somnolence only when the current exerted a destructive action.

(5) **PAVLOV'S THEORY.** Pavlov believes sleep and internal inhibition to be essentially one and the same process, i.e., sleep is simply the spreading (irradiation) of internal inhibition over the entire cortex with the subsequent involvement of subcortical levels; and internal inhibition confined within the boundaries of a single analyzer is a localized sleep. He was led to this conclusion by

the behavior of animals during his investigations of conditioned reflex action. Drowsiness and sleep were frequent accompaniments of all forms of internal inhibition, e.g., inhibition of extinction and of delay (p. 910), conditioned and differential inhibition, or the inhibition which ensued spontaneously after the repetition of positive conditioned reflexes over a long period of time. An animal, for example, which is quite alert during the establishment of a reflex to a definite musical tone becomes drowsy and falls asleep in the stand during attempts to develop differentiation (p. 911) of a closely similar tone; its muscles relax, it may snore loudly and other positive conditioned stimuli fail to awake it. Moreover, drugs such as caffeine (p. 916) which reduce internal inhibition, and those such as bromides which increase it, have corresponding effects upon the mechanism of sleep. As mentioned previously, positive conditioned reflexes after having been repeated over a long period ultimately undergo inhibition. At this stage in the investigations the experiment is frequently terminated by the animal falling asleep. Experiments involving the use of thermal and tactile stimuli are most frequently interrupted by the onset of sleep; auditory conditioned stimuli are the least likely to have this effect.

Protracted, mild stimulation of an extraneous nature has also been found to cause cortical inhibition and lead to sleep. It has been mentioned (p. 909) that an extraneous stimulus induces inhibition, through setting up an investigatory reflex; upon repetition, the inhibitory effect disappears, and the conditioned responses return. With further repetition, however, the extraneous stimulus again causes inhibition; this time, it exerts, of itself, a direct inhibitory effect upon the cortex.

Pavlov's theory has much to recommend it. The drowsiness which results from some oft-repeated form of monotonous stimulation, e.g., reading or being read to in a low even voice, a dull lecture, or boredom from whatever cause, is well known. Also, the preparations for sleep—the various agencies in a familiar environment—probably serve themselves as inhibitory conditioned stimuli. A dog, for example, which has fallen asleep during previous experiments may go to the same when merely brought into the room where the experiments had been performed or when preparations are being made to repeat them. The customary hour for retiring probably acts also as a time conditioned stimulus.

In some experiments described by Pavlov the inhibitory process involved the cortex but did not descend to subcortical levels governing equilibrium and the postural reactions of the skeletal muscles. The animal assumed a trance-like or cataleptic state in which muscular tone was retained, the general attitude being one of alertness. It stood with wide-open eyes but was quite unresponsive to all ordinary forms of stimulation. Pavlov looks upon this state as a transition stage between wakefulness and deep sleep, due to a less widespread diffusion of the inhibitory process, and similar in nature to hypnosis. It is suggested that during sleep, also, all cortical areas, analyzers as Pavlov terms them, are not necessarily under the inhibitory influence. The alertness of a mother, apparently in deep sleep, to the slightest noise made by her baby, is a case in point. In such an instance it is the auditory area or analyzer which has remained apparently outside the inhibitory influence.

These observations have undoubtedly some bearing upon the production of *dreams*. Dreams are evidently due to cortical activity since they involve memory and the ability to associate various sensory impressions. It is apparent, however, that it is the less critical areas of the cortex, i.e., those endowed with relatively crude analyzing and synthetic abilities, which are involved. The illogical, uncritical and often grotesquely absurd character of dreams is well known, yet the mental pictures are often drawn with great vividness, and a stimulus which in the waking state would leave little imprint upon consciousness is sometimes magnified enormously during sleep. As Descartes says, "A flea bit me and I dreamt of a sword cut!" Sensations arising in the viscera, such as those due to hunger, a distended stomach or bladder, thirst, etc., which during the day may cause no more than a passing thought may give rise to dreams filled with the most exciting events. It has been mentioned that dreams occur only during light sleep, that is, at a time when one would expect the internal inhibitory process to be restricted to the more highly specialized parts of the analyzers and before it has spread to involve the entire cortex. Dreaming may therefore be reasonably looked upon as being dependent upon a state of partial sleep—certain areas of the cortex being freed from the restraint which during the day is exercised by more critical regions.

(6) KLEITMAN'S THEORY. Kleitman has published a number of papers in the last few years on the subject of sleep. According to him, sleep is due to the inactivity of the cerebral cortex resulting from a reduction in the number of afferent impulses, especially from the muscles, reaching the sensorium. Fatigue of the neuromuscular mechanism mediating muscle tone, with consequent suppression of impulses from muscle proprioceptors, is considered to be the most important factor in the onset of sleep. According

to this author loss of muscle tone is an invariable prelude to sleep.

Kleitman claims to have demonstrated a diurnal variation in the speed, accuracy and steadiness with which certain muscular acts are performed. The efficiency of performance was maximal in the afternoon and minimal late at night and in the early morning. It is suggested that the variability is due to a corresponding rhythm in the tone of the skeletal musculature. But quite apart from these experiments, many observations give credence to the theory that cortical inactivity resulting from the blockage of afferent impulses is an important element in the onset of sleep. The exclusion of stimuli from visual, auditory and cutaneous receptors and the diminution of the flow of proprioceptor impulses as a result of muscular relaxation, are well-known means employed to induce sleep, whereas cortical activity, whether from psychic causes—*anxiety, worry, excitement, etc.*—or as a result of impulses set up in exteroceptors or muscle receptors, prevents sleep. In extreme fatigue when muscle tone is presumably at a minimum and the threshold of other afferent paths also probably raised as well, sleep comes on irresistibly. Kleitman and his associates found that after a prolonged period of wakefulness the only way in which they could keep from falling asleep was by moving about, or at least remaining in a standing or sitting position. Upon lying down and permitting their muscles to relax they were immediately overpowered by sleep.

An attempt has been made by Kleitman to reconcile the cortical theories of sleep with the undoubted fact that the hypothalamus is in some way concerned in the sleep process.

That sleep is not solely dependent upon the cortex is evident from the fact that decorticated dogs show periods of sleep alternating with intervals of wakefulness. The sleep rhythm in these animals is not, however, related in any way with night and day but consists of a number of shorter or longer periods throughout the twenty-four

hours. The sleep periods occur most constantly after feeding. During the waking periods the animals walk around almost incessantly. Lower orders in the animal scale in which the cortex is rudimentary and which, in consequence, are unable to develop a wide variety of conditioned responses show a similar sleep rhythm. This more primitive sleep mechanism is dependent conceivably upon a center located at a subcortical level, and most probably in the hypothalamus. We may regard it as presiding over vegetative functions and acting continuously to keep the animal asleep unless inhibited by impulses arising out of the more primitive processes and reactions, *e.g., hunger, thirst, cold or distension of the bladder or rectum.*

The diurnal sleep rhythm, that is, the ability to keep awake throughout the day, is dependent, on the other hand, upon the development of conditioned reflexes. So long as the cortex can bring its analyzing ability to bear upon the stream of impulses received from the different distance receptors, muscles, skin, etc., the functions of the primitive sleep center are held in abeyance. With the spread of internal inhibition over the cortex, or as a result of the elimination of stimuli from the periphery, the center asserts itself, and the subject is unable to remain awake. The diurnal sleep rhythm is therefore an acquired phenomenon—not inborn. Infants and very young animals do not show it but, like decorticated animals, have several sleeping periods throughout the day.

Those who believe that sleep results from the inhibition of a waking center in the hypothalamus take a somewhat different view. According to them sleep is a negative rather than a positive state, that is, it is due to the inactivity of the waking center. The activity of this center it is conceived is maintained by impulses received from the cortex. Cortical function is dependent in turn upon a flow of impulses along various afferent channels.

CHAPTER LXXI

THE CEREBELLUM

GENERAL STRUCTURE AND DIVISIONS

The cerebellum consists of a narrow central body, the *vermis* (or worm) and two lateral masses, the *right* and *left cerebellar hemispheres*. On its upper surface the demarcation between the vermis (*superior vermis*) and the hemispheres is slight. Upon the under surface the hemispheres are separated by a deep depression—the *Uccula*; the floor of the latter is formed by the inferior surface of the vermis. The inferior aspect of the vermis (*inferior vermis*) consists of four subdivisions, these are called in order from before backwards the *nodule*, *uvule*, *pyramid* and *tuber*. On either side and continuous with the nodule, is an elongated, somewhat lobulated structure called the *flocculus*. The cerebellar surface is not convoluted like the cerebral cortex but is divided by parallel and curved furrows into numerous *pinnae* or *folia*. The total cortical area of the human cerebellum is about 100,000 sq. mm., or less than half that of the cerebral cortex.

Though the division of the cerebellum into the vermis and two hemispheres possesses considerable descriptive value, comparative neurologists (chiefly Bolk, Ingvar, Elliott Smith and Larsall), have suggested other divisions which possess greater significance from a phylogenetic and functional point of view. In Larsell's description (see fig. 382) the cerebellum is divided into two fundamental or primary parts, (a) the *flocculonodular lobe* or *vestibulo-auricular part*, and (b) the *corpus cerebelli* which is predominantly concerned with the integration of proprioceptive impulses (from the muscles). These two parts are separated by a deep fissure—the *posterolateral fissure*—which is present in all vertebrate brains.

The *flocculonodular lobe* which comprises the *flocculus* and the *nodule* is developed from the structures in the region of the vestibular nuclei. The *corpus cerebelli* includes all the rest of the cerebellum, i.e., the portion lying above and in front of the posterolateral fissure. It is subdivided by a well-marked fissure—the *fissura prima* (of Elliott Smith)—into an anterior and a posterior lobe. The *anterior lobe* consists of three subdivisions; the *lingula*, *lobulus centralis* and *culmen*. The *posterior lobe* includes the *lobulus simplex*, *declive*, *pyramid* and *uvule*, together with the associated parts of the hemispheres (*lobulus ansiformis* and *lobulus paramedianus*, see below) and the *parafocculus* (fig. 382). The *flocculonodular lobe* (vestibular function), the *anterior lobe* of the *corpus cerebelli*, and the *nodule*, *pyramid* and *parafocculus* of its posterior lobe are physiologically old (*paleocerebellum*). The remainder of the cerebellum, namely, the greater part of the hemispheres, and the *superior vermis* are later

acquisitions (*neocerebellum*), appearing coincidentally with the development of the pyramidal tracts. The *neocerebellum* is absent or rudimentary in submammalian forms.

The small compact mass situated on either side of the inferior vermis is known as the *tonsil* or *paramedian lobule*, and that lying immediately behind the *fissura prima*, as the *lobulus simplex*. The remainder of the hemisphere belonging to the posterior lobe of the *corpus cerebelli* is known as the *ansiform lobule*. The latter shows its greatest development in the human brain, its function apparently being concerned with the tonus adjustments required in the performance of skilled muscular movements.

INTERNAL STRUCTURE

When sectioned in the sagittal plane each hemisphere of the cerebellum presents a branching core of white matter which from its foliage-like appearance, has been named the *arbor vitae*. The terminal branches of the white matter are covered with a coating of gray substance which constitutes the cerebellar cortex. The leaf-like structures so formed are spoken of as *folia*, and are responsible for the laminated appearance of the cerebellar surface (fig. 383). Unlike the cortex of the cerebrum the cerebellar cortex shows a uniform histological structure throughout its extent.

The gray matter

THE CORTEX. Three cell layers are distinguished.

(1) *The molecular (or plexiform) layer* is outermost and consists largely of unmyelinated nerve fibers derived from (a) the white substance, (b) the cells of the two underlying layers, and (c) the cells within this layer itself. The cells of the molecular layer are arranged in a deep and a superficial stratum, their axons synapse with the Purkinje cells, whose dendrites arborize throughout this layer. The cells of the superficial stratum are small, star-shaped and few in number. The deep stratum is composed of larger stellate cells whose axons run transversely in relation to the long axis of the folium and arborize by means of collaterals around the bodies of several Purkinje cells. They are referred to as "basket" cells (see fig. 384).

(2) *The intermediate layer of Purkinje cells.*

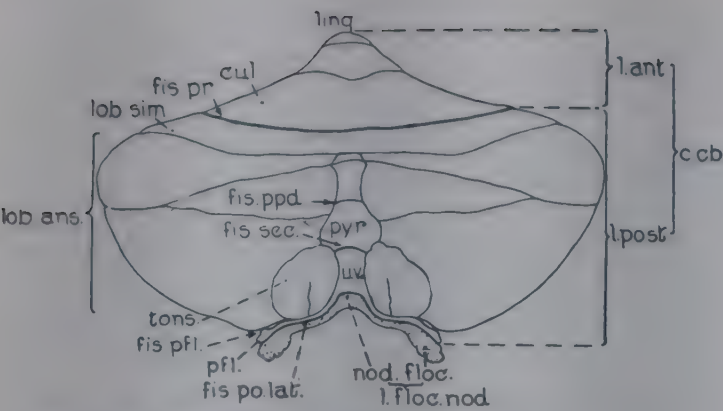


FIG. 382. Diagram of the cerebellum showing its division into a flocculonodular lobe (stippled area) and a corpus cerebelli (blank area) consisting of an anterior and a posterior lobe. (After Larsall.)

The large flask-shaped bodies of these cells, which are peculiar to the cerebellum, form a layer between the molecular and the granular layers. Their dendrites pass outwards into the molecular layer where they arborize luxuriantly; as just mentioned, collaterals of axons of the basket cells arborize around their bodies. The axons of the Purkinje cells enter the white substance, and end by synapsing with cells in the cerebellar nuclei. The Purkinje arborizations extend outwards through the entire thickness of the molecular layer. They are spread out or flattened in the transverse plane of the folium, thus resembling a vine trained

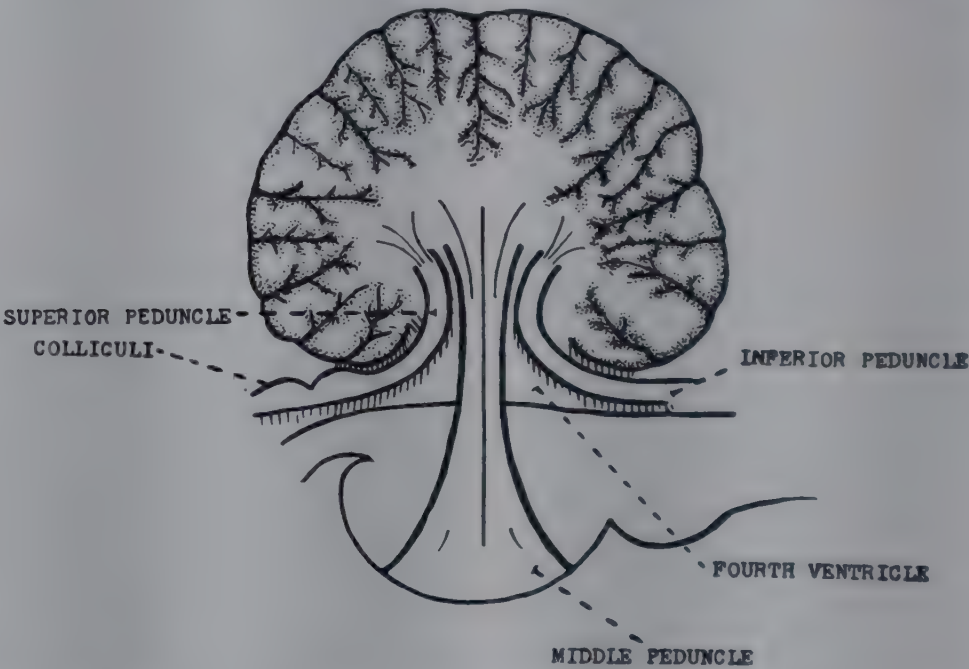


FIG. 383. Diagram of the cerebellar peduncles (redrawn from Villiger).

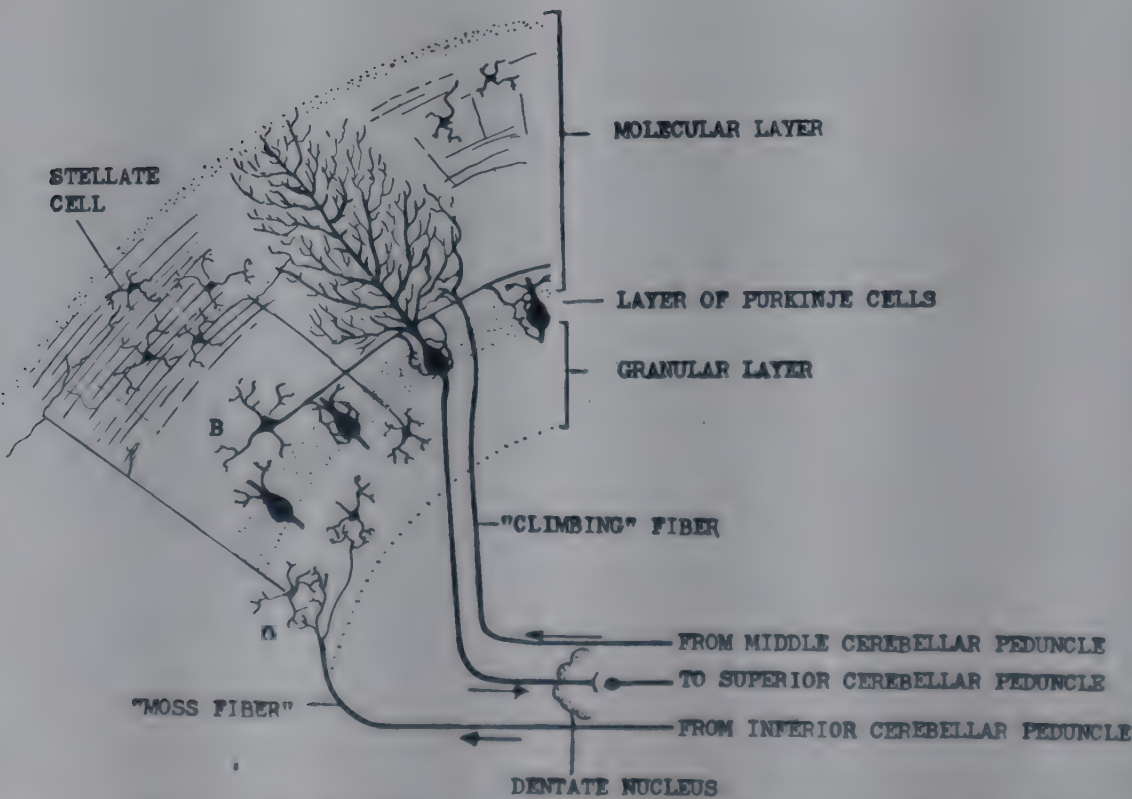


FIG. 384. Diagram to show structure of cerebellar cortex. G, granule cell; B, "basket" cell.

against a wall rather than a bush. The body of the cell is flattened in a similar manner.

(3) *The granular layer*, which rests upon the white matter, is composed of small, round, closely packed cells, and numerous nerve fibers. The cells possess four or five dendrites which end in a network of branches close to the cell body and connect with those of neighboring cells. One long process (axon) of each extends into the molecular layer where it connects with the dendrites of a large number of Purkinje cells. Afferent fibers ("moss fibers," p. 924) arriving via the inferior cerebellar peduncles make connections with the granule cells.

The cerebellar nuclei

The cerebellum contains on either side four separate gray masses. These are: (a) the *nucleus dentatus*, (b) the *nucleus emboliformis*, (c) the *nucleus globosus*, and (d) the *nucleus fastigii* (or *nucleus*) (fig. 385). The first three of these nuclei lie embedded in the white matter of the hemisphere. They receive the axons of Purkinje cells; their constituent cells give rise to fibers which leave the cerebellum via the superior cerebellar peduncles. The dentate nucleus is the most recently acquired of the cerebellar nuclei. Afferent fibers are derived mainly from the cortex of the hemispheres (lobus ansiformis). The roof nuclei are phylogenetically older than those of the other nuclei; they are situated in the white substance of the anterior part of the superior hemisphere, one on either side of the mid-line. They give off fibers from the cortex of the vermis (pyramis, uvula and nodule) and are closely associated with the vestibular nuclei to which they send, and from which they receive fibers, via the inferior cerebellar peduncles. The fastigial nuclei are regarded as centers for the integration of vestibular and spinocerebellar impulses. Fibers from the vestibular nuclei also pass to the nucleus emboliformis and nucleus globosus.

The white matter

The white matter of the hemispheres is composed of: (a) *projection fibers*, i.e., fibers which leave the cerebellum via the peduncles, (b) *association fibers*, which connect different regions of the same hemisphere, and (c) *commissural fibers* connecting cortical areas of the two hemispheres. The projection fibers—both afferent (to the cerebellum) and efferent (away from the cerebellum)—are in three bundles on each side which connect the cerebellum with the rest of the central nervous

system. These bundles are known respectively as the *superior*, *middle* and *inferior cerebellar peduncles*.

THE CEREBELLAR PEDUNCLES (SEE FIGS. 383 AND 386)

THE INFERIOR PEDUNCLES (RESTIFORM BODIES). Its fibers are predominantly afferent and convey non-sensory impulses from the labyrinth, joints and voluntary muscles. Its constituent fiber tracts are:

A. Afferent (entering) fibers

(1) *Dorsal spinocerebellar (direct cerebellar) tract*. The fibers of this tract end in the cortex of the anterior and posterior lobes of both sides but mainly of the same side. Some fibers also end in the nodule.

(2) *Dorsal external arcuate fibers* (p. 851) from the nuclei gracilis and cuneatus of the same side, and the *ventral external arcuate fibers* from the corresponding nuclei of the opposite side. These fibers end in the cerebellar cortex but their precise distribution is unknown.

(3) Fibers from the sensory nuclei of the *trigeminal*, *facial*, *vagus* and *glossopharyngeal nerves*.

(4) *Vestibulocerebellar tract* from the vestibular nuclei of the same side, and also directly from the vestibular nerve. They pass to the three cerebellar nuclei (nucleus globosus, nucleus emboliformis and nucleus fastigii) and are relayed to the cortex of the flocculonodular lobe and of the uvula.

(5) *Olivocerebellar tract* arising in the inferior olive of the opposite side and to some extent in the nucleus of the same side; the fibers of this tract end in the cortex of those portions of the vermis and hemispheres constituting the posterior lobe.

B. Efferent (leaving) fibers

(1) *Cerebellovestibular tract*. This is constituted of efferent fibers which arise from the nucleus fastigii, and end in the vestibular nuclei of the same side. Thence impulses may pass via (i) the vestibulospinal tract to the spinal centers and (ii) the medial longitudinal fasciculus to the nuclei of the ocular nerves and into the anterior ground bundle of the cord.

(2) *Cerebello-olivary tract* to the inferior olives of both sides. The latter are connected with the spinal centers through the olivospinal tracts (p. 856).

(3) Fibers to the reticular formation of the medulla from which impulses are relayed to (i) the motor nuclei of the cranial nerves, and (ii) spinal centers (via the reticulospinal tract).

THE MIDDLE PEDUNCLES (BRACHIA PONTIS) are also mainly afferent. Each contains:

(a) fibers which arise from cells of the pontine nuclei and end in the cortex of the posterior cerebellar lobe

(hemisphere) of the opposite side. These fibers constitute the secondary neurons of the *temporopontine-cerebellar* and the *frontopontine-cerebellar* tracts; (b) fibers which pass from the cerebellar nuclei to the hemisphere of the opposite side (see fig. 386).

THE SUPERIOR PEDUNCLES (BRACHIA CONJUNCTIVAE) enter into the formation of the upper part of the roof of the 4th ventricle and plunge into the mid-brain just beneath the inferior colliculi. The superior cerebellar peduncle contains both efferent and afferent fibers but is composed predominantly of the former. It is through the superior peduncle that the cerebellum exerts its main influence upon the skeletal musculature.

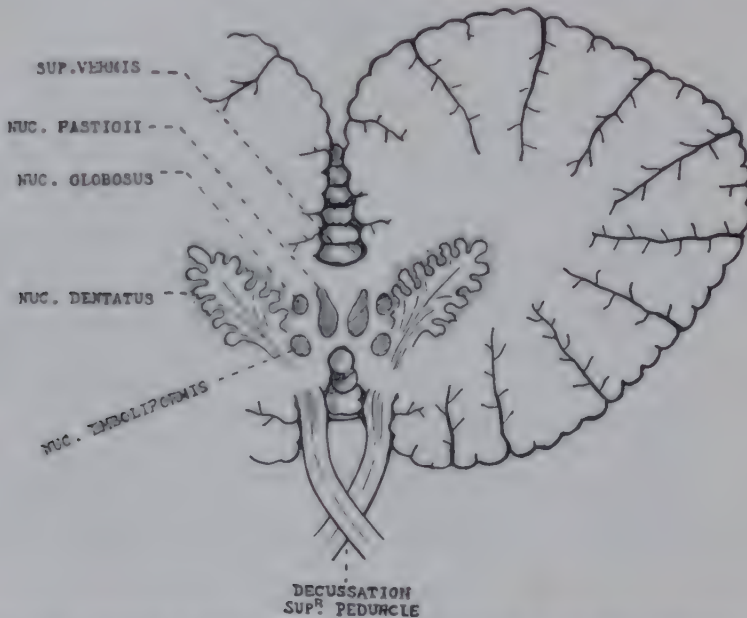


FIG. 385. Diagram of a horizontal section through the cerebellum to show the cerebellar nuclei (viewed from in front).

A. *The efferent fibers* arise from all the cerebellar nuclei with the exception of the nucleus fastigii. The Purkinje cells constitute the primary neurons of these paths. The fibers decussate in the mid-brain with those of the opposite side and then divide into an ascending and a descending group.

(1) *The ascending fibers:* (a) terminate in the nucleus parvocellularis and nucleus magnocellularis of the red nucleus; impulses from the large-celled nucleus are relayed via the rubrospinal and the rubrobulbar tracts to the cranial nuclei and the spinal centers of the opposite side; (b) pass to the lateral part of the lateral nucleus of the thalamus and are relayed to the cerebral cortex.

It will be noted that the ascending fibers connect one cerebellar hemisphere with the red nucleus, thala-

mus and cerebral cortex of the opposite side, but, as a result of the crossing of the rubrospinal and pyramidal (corticospinal and corticobulbar) tracts, each cerebellar hemisphere is ultimately connected with the same side of the brain stem and spinal cord.

(2) *The descending fibers* terminate around cells of the reticular formation of the pons, medulla and cervical cord.

B. *The afferent fibers* of the superior cerebellar peduncle are:

(1) The ventral (indirect) spinocerebellar tract. This ascends through the medulla and pons and reaching the upper level of the latter turns backwards, arches over the peduncle, enters the anterior medullary velum, and passes within this to the cerebellum.

The fibers end in the cortex of the anterior lobe mainly of the same side.

(2) *The tectocerebellar tract*, composed of fibers which originate in the superior colliculus. It probably conveys retinal impulses and so constitutes a pathway for visuocerebellar reflexes. This tract has not been demonstrated in man.

The fibers reaching the cerebellar cortex via the peduncles are of two main types: (a) "*moss fibers*," which end in moss-like appendages around the cells of the granular layer (fig. 384) and (b) *climbing fibers*, which pass outward to the molecular layer; here they give off collaterals resembling the tendrils of a vine which appear to cling to the arborizations of the Purkinje cells. According to Caja the

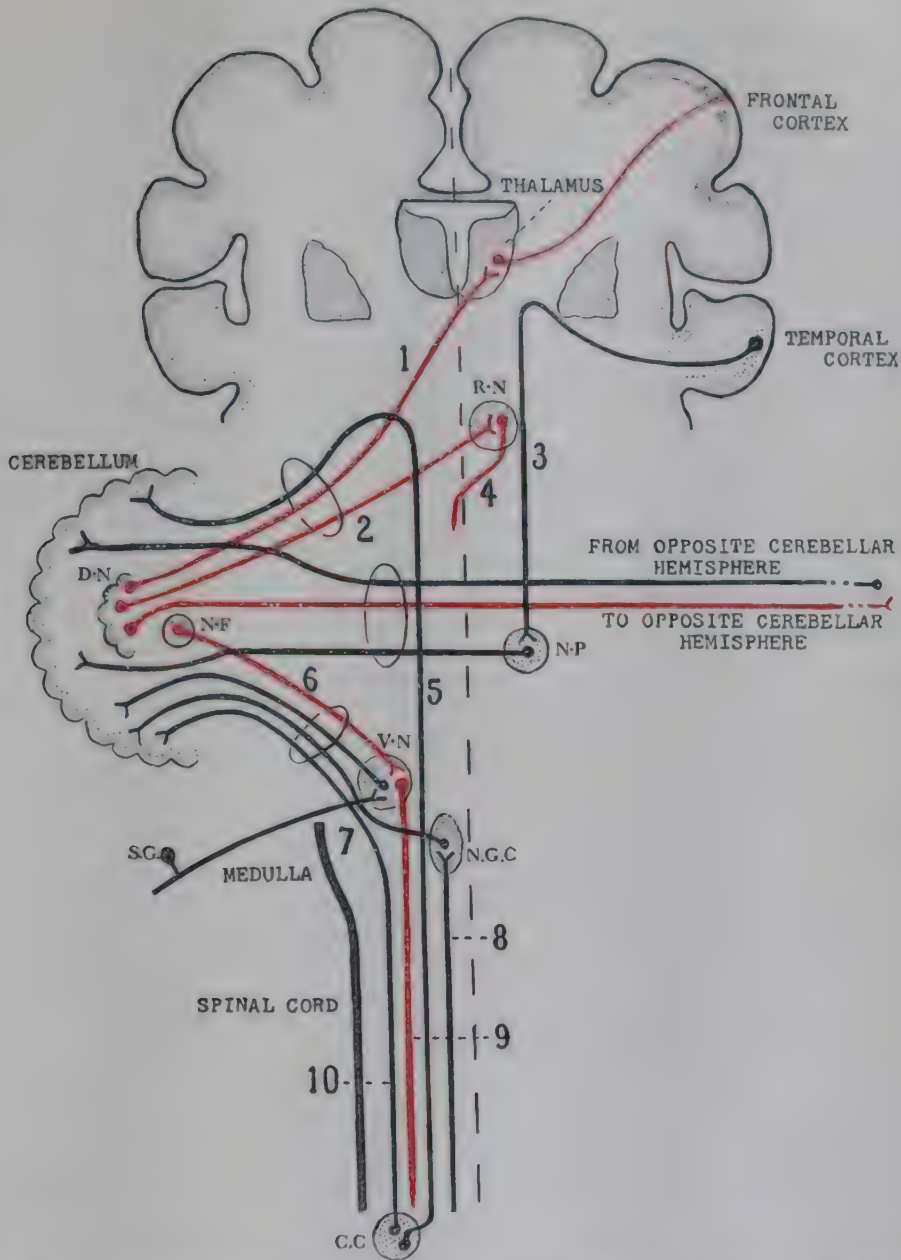


FIG. 386. Diagram of chief cerebellar connections. Afferent fibers, black; efferent fibers, red. R.N., red nucleus; D.N., dentate nucleus; N.F., nucleus fastigii; N.P., pontine nuclei; V.N., vestibular nucleus; N.G.C., nuclei gracilis and cuneatus; S.G., cell of Scarpi's ganglion; C.C., Clarke's column (dorsal nucleus). 1, cerebello-thalamic tract; 2, cerebellorubral tract; 3, temporo-pontine tract; 4, rubrospinal tract; 5, ventral (indirect) spino-cerebellar tract; 6, cerebellovestibular tract; 7, external arcuate fibers passing from N.G.C. to cerebellum; 8, fasciculi gracilis and cuneatus; 9, vestibulospinal tract; 10, dorsal (direct) spinocerebellar tract.

climbing fibers are derived from the vestibular and pontine nuclei; while the direct spinocerebellar and olivocerebellar tracts are constituted of moss fibers. Through their connections with the cells of the granular layer each moss fiber is connected indirectly with a large number of Purkinje cells, whereas a climbing fiber is in communication with only one or two Purkinje cells.

THE EXPERIMENTAL STUDY OF THE CEREBELLUM EFFECTS OF EXCISION OF THE CEREBELLUM AND OF SECTION OF THE PEDUNCLES

Luciani's extirpation experiments are classical. This observer has described the results of his operations upon dogs and monkeys as occurring in three stages.

In the *first stage* or "*dynamic phase*" which lasts for from 6 to 10 days the animal showed restlessness and agitation and, when the cerebellar removal was complete, increased tone of the muscles on both sides of the body. There were also observed *extension and abduction* of the forelimbs, *clonic movements* of the hind limbs, *retraction of the head with hyperextension of the back* (opisthotonos) and *convergence of the eyes*. *Horizontal nystagmus* also occurred in some cases. In the monkey the effects upon the neck and back muscles caused the animal to *fall backwards* when it attempted to assume an erect position. Unilateral ablation was followed by tonic spasm of the muscles on the operated side with consequent curvature of the body with its concavity towards that side (pleurothotonos), rotation of the head and neck and of the body around its long axis towards the healthy side, and tonic extension of the ipsilateral forelimb with clonic movements of the other three limbs. After unilateral ablation there may also be slight nystagmus and a squint with downward and inward deviation of the eye on the operated side, and outward and upward deviation on the healthy side (*skew deviation*). These effects of the dynamic phase are probably release phenomena, i.e., the result of the sudden removal of cerebellar inhibitory influences upon other mechanisms (e.g., labyrinthine) governing muscle tone and not, as might be thought, the result of the irritation of divided nerve tracts.

The *second stage* is marked by "deficiency" phenomena; that is to say, the overactivity of other parts of the nervous system, as a result of their release from cerebellar influence, has largely disappeared and symptoms, which depend more directly upon the loss of cerebellar function (p. 928), become more prominent. This stage has been analyzed by Luciani into three components to which he has given the names (a) *asthenia*, (b) *atonia* and (c) *astasia*.

By *asthenia* is meant the muscular weakness which in the earlier part of the second stage renders the animal unable to stand. There is no actual paralysis, however, for the animal is able to swim well and with perfect coördination, since the weight of the body is then supported by the surrounding water.

Under the term *astasia* is included the unsteadiness of the muscles, which gives rise to coarse involuntary effort, they are therefore referred to as *intention tremors*. Other manifestations of cerebellar deficiency are jerkiness and incoördinate action of the muscles (*asynergia*, p. 929). The gait when the animal first recovers its ability to walk is reeling or staggering in character; the head pendulates or oscillates from side to side. When the ablation is unilateral the muscular defects on the operated side cause the animal to fall to that side. As a result of the lowered muscular tone on

the operated side the body is curved towards the healthy side. The animal in consequence while swimming or walking tends to circle towards this side.

The defects in voluntary muscular control, namely, the tremor, the asynergic action of the muscles and the abnormalities of gait are referred to collectively as *cerebellar ataxia*.

In the *third stage* compensation develops. There is a gradual diminution of the deficiency phenomena (organic compensation) together with abnormal movements directed towards counteracting or neutralizing the effects of the cerebellar deficiency (functional compensation).

Cerebellar removal causes no effect upon consciousness or upon any form of sensation.

EFFECTS OF SECTIONING THE PEDUNCLES. Division of all three peduncles of one side causes defects identical with those following unilateral cerebellar ablation. *Asynergia*, *fatiguability* and *hypotonia* of the muscles, together with a coarse *tremor*, appear on the same side as the lesions. Somewhat similar though less severe effects follow the severance of one superior cerebellar peduncle. Compensation occurs through the remaining cerebellar connections (Walker and Botterell), especially through the corresponding peduncle of the opposite side. Even after unilateral section of the three peduncles, compensation is brought about after a time through the remaining half of the cerebellum and through the frontal lobes (Botterell and Fulton).

The experiments of Aring and Fulton indicate that the nervous mechanism involved in the production of the tremor lies in the excitable part of the cerebral cortex (area 4 and the upper part of area 6a); removal of these areas after contralateral section of the cerebellar peduncles abolished the tremor. The ability to compensate for cerebellar defects depends, apparently, upon the premotor area (area 6a, upper part). Removal of this area was followed by marked accentuation of the cerebellar signs and permanent impairment of the animal's ability to compensate for the cerebellar defect. These findings suggest that the "cerebellar" signs which are sometimes seen clinically in lesions of the frontal lobe are probably due to involvement of the premotor cerebellar connections (frontopontine-cerebellar tract). On the other hand, removal of the motor area (area 4) alone, temporarily abolished and permanently depressed the manifestations of cerebellar deficiency.

CEREBELLAR LOCALIZATION AS DETERMINED BY REGIONAL STIMULATIONS AND ABLATIONS. Localization in the cerebellum appears to be on a purely functional basis. That is to say, the cerebellum, unlike the motor area of the cerebral cortex, cannot be mapped out into circumscribed regions, each correlated with the movements of a discrete group of muscles in some one or other part of the body. The most that can be said for an anatomical or spatial relationship between the cerebellum and the peripheral parts of the body is that it exerts its influence mainly ipsilaterally, i.e., a given half of the cerebellum acts predominantly upon the muscles of the same side of the body, that the anterior lobe exerts an influence upon the postural musculature of the head and neck, the ansiform lobe affects the muscles of the upper limb and the uvule and pyramid the muscles of the trunk. The hemispheres are concerned mainly with the integration of voluntary movements.

In the decerebrate animal a weak faradic current applied to the cortex of the *anterior lobe* of the corpus cerebelli causes a reduction in extensor rigidity on the same side. The effect is most pronounced in birds. It is quite evidently due to stimulation of the cortex itself and not to the spread of the current to deeper structures (e.g., nuclei) since the response is annulled by cortical anemia or by the application of cocaine. Miller and Banting observed, occasionally, walking movements upon weak stimulation of the superior surface of the vermis (anterior lobe) which suggests that this part of the cerebellum exerts an excitatory as well as an inhibitory influence.

Excision of the cortex of the *anterior lobe* enhances postural mechanisms, increasing the stretch reflexes (p. 822) and the positive supporting reactions. The responses of the antigravity muscles are exaggerated. Hyperactivity of the extensors of the back causes extreme opisthotonus. Excision of any part of the anterior lobe (with the exception of the lingula) does not cause any noteworthy disturbance of gait or balance.

Electrical stimulation of the cortex of the hemispheres causes no obvious excitatory or inhibitory effect, though a rise in excitability of the motor area of the cerebral cortex can be induced by this means, and Miller found that the application of a 1 per cent solution of strychnine to the surface of the cerebellar hemisphere caused increased extensor tone and clonic movements of the limbs, chiefly of the same side. The effects following unilateral excision of one hemisphere (monkey) or its decortication are surprisingly slight, consisting of

hypotonia, some difficulty in the execution of skilled muscular acts and disturbances of gait (Botterell and Fulton). These defects involve both limbs on the same side as the lesion and are transient, persisting for only a few days (1 to 2 weeks). Similar effects, but more pronounced, followed bilateral excision of the hemispheres and in addition a slight tremor which lasts for a day or two. Botterell and Fulton conclude that the restoration of function is due to compensation through other parts of the cerebellum. Keller and his colleagues, on the contrary, found that complete bilateral removal of the cortex of the neocerebellum (p. 921) in dogs and monkeys caused no functional disturbance, even of a transitory nature, and concluded that when such effects do appear they are due to coincident injury of other cerebellar parts and that the "*neocerebellum is not essential for any of the functions that have been attributed to the cerebellum.*"

Ablation of the *nodule* and *flocculus* (flocculonodular lobe, p. 921) in monkeys or of the nodule and part of the uvule (Dow) which causes injury to vestibular paths, is followed by pronounced disturbances of balance. In man a lesion of this part of the vermis is also associated with disturbances of equilibrium. e.g., "forced" falling. Removal of the *nodule* alone in monkeys is followed by oscillation of the head and neck (and, in some instances of the whole trunk) forced falling backwards and an abducted gait. Ablation of the *uvule* alone is followed by some transient disturbance of equilibrium but destruction of the *pyramid* causes no defect of balance. But this part of the cerebellum is concerned in some way with vision. Its loss in the monkey results in an inability to halt its forward progression in time to prevent it from crashing into some obstacle. Faradic stimulation of the pyramid elicits an upward movement of the eyes, and Fulton suggests from this fact and the preceding observation the possibility of the pyramid being concerned in some way with the integration of proprioceptive impulses essential in judging distance.

STIMULATION OF THE CEREBELLAR NUCLEI

The following is a summary of the results obtained by Miller and Laughon.

(a) Faradic stimulation of the *nucleus dentatus* causes increased tone of the flexor muscles of the ipsilateral limbs (biceps brachii and tibialis anticus) together with inhibition of the tone of the extensor muscles (lateral head of the triceps, gastrocnemius and soleus). There is increased tone of the trunk muscles

of the stimulated side with consequent curvature of the body. There is no after discharge in the case of the limb flexors; "rebound" occurs in the extensors after cessation of the stimulation.

(b) Stimulation of the nucleus emboliformis, globosus or fastigii causes similar but more intense responses. Ocular movements may occur. In the case of the nucleus fastigii strong flexion of both forelimbs may result.

The efferent pathways for these reactions are via the superior peduncle, red nucleus and rubrospinal tracts in the case of the nuclei dentatus, emboliformis and globosus, and through the inferior peduncle, vestibular (Deiter's) nucleus and vestibulospinal tract in the case of the nucleus fastigii.

THE FUNCTIONS OF THE CEREBELLUM

The similarity between the effects of labyrinthectomy and cerebellar lesions, taken together with the intimate anatomical connections between the cerebellum and the vestibular nuclei, would naturally lead one to suppose that the primary function of the cerebellum is the maintenance of equilibrium. It seems clear, however, that the cerebellum is not concerned specifically with this function. Magnus and his associates have shown that all the labyrinthine and other righting reflexes can be carried out unaltered after complete removal of the cerebellum. It appears indeed that the cerebellum actually exerts an inhibitory influence upon the labyrinthine reflexes since Pollock and Davis found them to be more active after decerebellation. Luciani, who denied that the function of the cerebellum was one concerned primarily with the maintenance of equilibrium of the body and its orientation in space, attributed the disturbances of posture simply to weakness, hypotonia and incoördination of the muscles (p. 926). He pointed out that the blindfold decerebellate dog swims with good orientation, when thrown into water. The blindfold labyrinthectomized animal (cerebellum intact), when treated similarly, drowns (p. 831). It is not now believed that the cerebellum exerts any specific or direct effect in coördinating the actions of the different muscles engaged in a voluntary movement, i.e., of timing their contractions. The jerkiness and irregularity of muscular action seen in cerebellar disease and which is referred to as ataxia, is thought to be largely due to the weak and hypotonic state of the muscles rather than to a failure of coördination. "It will not suffice to speak of coördination as a separate faculty, coördination is the function of the whole and every part of the nervous system" (Hughlings Jackson).

What then are the functions of the cerebellum?

We have seen that it receives non-sensory impulses from the muscles of the limbs, trunk, face, etc., and from the labyrinth, and that it is connected in turn with the muscles by efferent tracts. The cerebellum has been described as "the head ganglion of the proprioceptive system" (Sherrington). This does not mean, however, that it is a center through which the various postural reflexes are actually carried out. The augmentation of the labyrinthine reflexes after cerebellar removal, and the fact that decerebrate rigidity is not abolished after decerebellation but is inhibited by stimulation of the cerebellar cortex, provide evidence to the contrary. Moreover, tonic and phasic reflexes and regular rhythmic reflexes are carried out in the decerebrate animal after cerebellar removal.

The cerebellum exerts, rather, a modifying or regulating influence upon muscular activity whose primary centers are situated in other parts of the brain or in the spinal cord. Through its connections with the motor neurons of the brain and cord the muscles receive impulses of either an inhibitory or an augmentor nature, depending upon the conditions at the moment. Through these connections those finer adjustments of tone and the appropriate distribution of tone between groups of muscles which are essential for the maintenance of posture and for the accomplishment of complicated and precise voluntary movements are brought about. In other words, upon the general background of tonus established through centers in the cord or brain the cerebellum makes the final delicate adjustments which enable the various muscle groups to act smoothly and harmoniously, i.e., as a coöperative whole, in a given movement.

Following Beevor, the muscles concerned in a voluntary muscular act may be classed in three groups:

(a) PRIME MOVERS OR AGONISTS, those whose contraction is essentially responsible for the movement of the part.

(b) ANTAGONISTS, those which oppose the prime movers.

(c) SYNERGISTS, those which assist the prime mover and reduce unnecessary movements to a minimum.

(d) FIXATION MUSCLES, those whose contraction causes the fixation of the neighboring joints and maintains the limb or body in a position appropriate for carrying out the particular movement.

Normally these muscle groups act as a unit. The contraction of the prime mover, e.g., the biceps, is accompanied by inhibition of the contraction of its antagonist, i.e., the triceps. The re-

al inhibition, however, is not absolute; the antagonistic muscle as shown by Tilney and Pike, gives a coincident but weaker contraction, and thus serves the function of a "brake" or "snubber" to check the action of the agonist. At the same time the fixation muscles of the neighboring joint contract, thus enabling the agonist to exert its force with a minimum of waste effort. Any increase in the force of contraction of the agonist is accompanied by a corresponding rise in tone of its opponent (antagonist). Also, the muscles of fixation and the synergists contract more powerfully as the contraction of the prime movers increases, while groups of fixation muscles and synergists, which in weaker movement remain quiescent, may be called into play. To give an example, when the fingers are closed with moderate force the only fixation muscles which show activity are the extensors of the wrist. When, however, the fist is clenched forcibly, muscles of the elbow and even those of the shoulder contract to fix these joints. Through such action between the various muscles taking part in a given act, smoothness and steadiness of movement are ensured and muscular force thereby economized. After destruction of the cerebellum these nice coöperative actions are lost. The asynergia results in jerkiness, overaction and imperfect muscular control (ataxia).¹

Since it is in the conscious and not in the decerebrate animal that cerebellar removal shows its outstanding effects, it seems clear that the cerebellum is concerned mainly with voluntary movements, and with those semi-voluntary or automatic movements which are the basis of postural adjustments. It is the chief assistant of the higher motor centers. In order to be of full assistance it must, on the one hand, be in communication with labyrinthine and muscle proprioceptors (vestibulocerebellar and nococerebellar tracts) and, on the other, be informed of the "intentions" of the cerebral cortex. The cerebropontine-cerebellar tracts provide the probable paths along which intelligence of the projected plan of the cortex in any voluntary movement is transmitted to the cerebellum. The cerebellum sends messages in turn through its superior olivuncles to the cerebral cortex (via the thalamus) which may reinforce or strengthen, and perhaps modify in other ways, the discharge from the motor

Holmes denies that the cerebellum exerts any specific function in respect to the distribution of tone among various muscles acting synergically. The steady action which tonic muscles normally exert on their antagonists is absent in cerebellar disease but Holmes maintains that this is due merely to the general atonicity.

area itself. It is probably through the cerebello-rubro-spinal pathway that the cerebellum exerts its chief synergizing action upon the muscles, adjusting their tone, appropriately as to time, strength and distribution, to the voluntary discharge.

THE MANIFESTATIONS OF CEREBELLAR DISEASE

The signs of cerebellar disease are much more pronounced in acute lesions, e.g., abscess, hemorrhage or trauma, than in those, e.g., tumor, which develop more gradually. In slowly developing lesions or after the subsidence of acute cerebellar disease a certain degree of compensation for the cerebellar defect always occurs. The majority of the signs of cerebellar disease are the result fundamentally of asynergia of the voluntary muscles.

Following Holmes, the chief features of cerebellar lesions will be considered under the following headings: (1) *hypotonia*, (2) *asthenia, fatigability and slowness of movement*, (3) *tremor*, (4) *asynergia*, (5) *decomposition of movement*, (6) *dysmetria*, (7) *rebound phenomenon*, (8) *adiadochokinesis*, (9) *vertigo and past-pointing*, (10) *deviation of the eyes and nystagmus*, (11) *attitude and gait*, (12) *disturbances of speech*, (13) *reflexes*.

HYPOTONIA. This is usually a prominent feature in acute cerebellar lesions. The muscles are flabby. The limbs for this reason assume unnatural attitudes and can be moved passively into positions of extreme flexion or extension. The extremities flop about when shaken vigorously and, if the patient is suddenly rotated when standing, the arms swing loosely from the shoulders.

ASTHENIA, FATIGABILITY AND SLOWNESS OF MOVEMENT. The muscles on the affected side are definitely weakened and tire easily. The commencement of any voluntary movement is delayed, and both contraction and relaxation phases are abnormally slow. Neither hypotonia nor asthenia are notable features in chronic lesions and it is probable that in acute lesions hypotonia is not a result of the cerebellar defect itself but of the involvement of neighboring structures. It will be recalled that hypotonia was not observed by Magnus nor by Aring and Fulton after decerebellation. Some also question whether asthenia is a manifestation of cerebellar deficit, but Holmes considers it to be due to involvement of the cerebellar nuclei.

TREMOR. This is a coarse involuntary jerking which is increased by voluntary effort. It is due evidently to the loss of the steadying effect which

increased tonus of the antagonistic muscles normally affords to voluntary movements.

ASYNERGIA. It should be pointed out that this term as used by Holmes has a much more restricted meaning than that which is usually given to it. This observer applied the term especially to the asynchronism observed between the actions of the fixation muscles and the prime movers, as well as to the lack of coöperation which normally exists between the muscles of the limbs, trunk and neck during walking and standing, and other acts necessitating postural adjustments of the various members of the body against gravity. For example, when the patient is asked to clench his fist, the extensors which normally fix the wrist as the fingers are flexed, either contract too early, and so over-extend the joint, or too late. In the latter event the wrist is flexed as the fist closes. Also, the patient may fall when he throws his head back owing to his failure to flex his knees, and so maintain his center of gravity over his base. Similarly when he attempts to sit upon a low stool he may fall backwards because he cannot at the same time flex his trunk at the hips.

DECOMPOSITION OF MOVEMENT. The patient performs acts "by numbers," to use a military expression. When, for example, he is asked, as he lies in bed, to extend his arm vertically, and then to touch his nose with his forefinger, the latter movement is not performed naturally by simultaneously lowering the arm and bending the elbow. The extended arm is first lowered to the side; not until this position is reached is the elbow flexed and the finger brought to the nose.

DYSMETRIA is the lack of ability to adjust the force of the contraction necessary for the accomplishment of a given act. For example, when asked to touch a point with his finger the patient overshoots the mark or, less commonly, fails to reach it. Dysmetria in a lower limb may be demonstrated by the heel to knee test; when the patient, while recumbent, is directed to rest the heel of the affected side upon the opposite knee, he brings it in contact with the thigh or with the leg below the knee. Dysmetria is another manifestation of the general lack of synergic muscular control.

REBOUND PHENOMENON. If the patient is asked to attempt a movement against a resistance which is then suddenly removed, the limb moves forcibly in the direction towards which the effort was made. For example, if the observer holds the wrist of the patient, then asks him to bend the elbow, and, while he is making the effort, the forearm is sud-

denly released, flexion of the arm occurs with an unusual degree of force. This rebound phenomenon can be attributed to the absence of the "braking" action (p. 929) of the antagonistic muscles.

ADIADOCHOKINESIS (a = primitive; diadocho = succession, kinesis = movement) is the name given by Babinski to the inability to execute alternating movements rapidly, e.g., pronation and supination of the forearm, or flexion and extension of the fingers.

VERTIGO AND PAST-POINTING (pp. 841, 843). When the patient with his eyes closed is asked to raise the arm of the affected side and touch a prescribed mark the arm deviates outwards, rarely inwards. When directed to move the finger in the horizontal plane and touch the mark the arm in some cases, deviates upwards, in others downwards.

DEVIATION OF THE EYES AND NYSTAGMUS. In an acute unilateral lesion there may be conjugate deviation of the eyes to the uninjured side. When the patient is asked to look at an object in front of him the eyes move into position but then slowly deviate again to the uninjured side; after full deviation the eyes may return again to the central position with a sharp jerk. These alternate horizontal movements occur repeatedly and are known as nystagmus (p. 838). Though no deviation of the eyes is evident, nystagmus can sometimes be demonstrated in the subject of a cerebellar lesion when he is asked to turn his eyes towards either the injured or the uninjured side; the eyes are moved in the direction indicated and then deviate slowly towards the mid-line, only to be returned in a series of jerks toward the point in which he is attempting to look. The nystagmus is due to injury of vestibulo-cerebellar paths. (See also p. 845.)

Skew deviation of the eyes (p. 926) is sometimes observed in acute cerebellar disease.

ATTITUDE AND GAIT. Cerebellar disease sometimes results in abnormal attitudes. The trunk may be concave towards the affected side and sometimes rotated with the affected shoulder advanced. Rotation of the head with the chin towards the sound side, and flexed towards the shoulder of the affected side is not uncommonly seen in unilateral cerebellar disease. (This attitude is probably due to an associated lesion of the vestibular paths in the brain stem.) In standing the body is inclined towards the side of the lesion and tends to fall on that side. Falling backwards or forwards may occur (especially in lesions of the vermis). The abnormal attitudes of the limbs resulting from muscular hypotonicity when this is present, have been mentioned.

The gait is often staggering, reeling or lurching in character. The patient's line of travel is not straight but tends to be curved; the deviation is towards the affected side. When he is able to see his way he attempts to correct his tendency to deviate to one side by bringing himself back from time to time to his intended line of travel. Thus he follows a zig-zag course to his objective. The movements of the lower limbs are ataxic; they are often thrown about in an awkward, uncontrolled manner; the feet are raised unnecessarily high and brought down again clumsily, often in a clapping fashion.

Weisenburg has studied the gait of subjects of cerebellar disease by means of slow moving pictures. The gait was found to vary according to the muscle groups involved. When the muscles of the entire trunk are affected, the patient frequently is unable to stand or walk, and, when walking is attempted, the limbs are thrown out in almost any direction. If the muscles of the pelvic girdle alone are involved, the trunk is held rigidly erect and the lower limbs are thrown forward from the pelvis, the upper part of the body appearing to be led by the legs. When the shoulder girdle alone is involved there is less difficulty in standing or walking. The subject holds his legs wide apart and when walking, lurches in one or other direction, the upper part of the body leading and appearing to draw the legs after it.

DISTURBANCES OF SPEECH are due to asynergia of the muscles of phonation and articulation. It is seen most frequently in lesions of the vermis. The speech abnormality may be drawling, scanning, sing-song or explosive in type.

THE REFLEXES. The cutaneous reflexes are normal and the deep reflexes, with the exception of the knee jerk, show as a rule no marked departure from the normal. The knee jerk is not uncommonly pendular in character. That is to say, when the leg is hanging free a tap on the patellar tendon causes a slower, less brisk response than normal, but one of greater amplitude. Also, unlike the response of the sound side, the return excursion of the leg is not arrested when, as a result of the influence of gravity, it reaches the resting position, but swings beyond. Several to and fro movements follow before the limb finally comes to rest. This behavior is evidently due to the hypotonicity of the flexor and extensor muscles and thus to a lack of the restraining effect which they normally exert upon one another to prevent exaggerated excursions of the limb in either direction.

Muscle sense and other forms of sensation are unaffected in cerebellar disease. The following are the principal types of cerebellar lesion: (1) *Tumor*, (2) *abscess*, (3) *injury*, e.g., gunshot wounds, (4) *degenerations* of (a) the cerebellar cortex, (b) the middle and inferior peduncles, (c) more rarely, of the cerebellar nuclei and superior peduncles, (d) of the spinocerebellar tracts, e.g., Friedreich's ataxia, a hereditary condition.

A lesion involving the neocerebellum (superior vermis and hemispheres) is associated with hypotonia; dysmetria; weakness, slowness and irregularity of voluntary movement; tremor and nystagmus. In disease of the flocculonodular lobe, there are marked disturbances of balance with a swaying, staggering gait and a tendency to fall backwards.

CHAPTER LXXII

THE CEREBROSPINAL FLUID (C.S.P.)

The discovery of the cerebrospinal fluid is generally ascribed to Cotugno (*Liquor Cotunnii*) but the first clear description was provided some fifty years after Cotugno's report by Magendie (1825).

Anatomical considerations

The dural and the arachnoid membranes form the meningeal covering of the sac which contains the cerebrospinal fluid. The fluid circulates in the subarachnoid space which is for the most part narrow but is widened into spaces (*cisterna*) at several points. The principal dilatations are the *cisterna magna* below the cerebellum and above the medulla, the *cisterna pontis* on the ventral aspect of the pons and the *cisterna basalis*, which contains the circle of Willis. The subarachnoid space is lined with flattened epithelial cells and, at intervals, particularly in association with arachnoid villi, clumps of phagocytic cells called *meningocytes* which stain like the cells of the reticulo-endothelial system are found.

Site of formation

In 1853 Faivre reported the results of a histological study of the villous projections of the chorioid plexuses into the ventricles of the brain. He found evidence of secretory activity in the cells covering these vascular structures. While this observation served to turn the attention of physiologists from the concept of Haller and Magendie, who believed that the fluid was formed by the leptomeninges, the evidence that the chorioid plexuses are the principal structures concerned was not obtained until quite recently. While further histological and pharmacological studies gave additional support for this view, physiological experiments and observations on human cases have provided more conclusive results. Some of the more significant results will be cited: (1) When the aqueduct of Sylvius is occluded an internal hydrocephalus is produced (Dandy and Blackfan; Frazier and Peet); (2) during an operation on a human case a clear fluid was observed exuding from a choroid plexus (Cushing); (3) a sustained outflow of fluid, similar in volume to that obtained from the subarachnoid space was secured from a catheter inserted into the

aqueduct of Sylvius (Weed); (4) a unilateral internal hydrocephalus can be produced by obstructing one foramen of Monro (Dandy) but there is no excess accumulation of fluid when the chorioid plexus is removed from the lateral ventricle before the obstruction is produced. These points leave no doubt of the importance of the plexuses in the elaboration of the fluid but there is suggestive anatomical evidence that the perivascular space (Virchow-Robin), and the ependymal cells of the ventricles and the spinal canal may participate to some degree in this process. Each blood vessel entering the nervous system is surrounded by a channel lined for a distance, varying with the caliber of the vessel, with mesothelial cells. The perivascular spaces were at one time thought to be connected with the lymphatic system but there is no evidence for this. The spaces can be traced along the blood vessels until a direct communication with nerve cells is demonstrated. This large perivascular area provides a means of communication for fluid between the subarachnoid space and nervous tissue.

Circulation

The fluid formed in the lateral ventricles passes through the foramen of Monro to join that produced in the third ventricle and thence through the aqueduct of Sylvius to the fourth ventricle. There is little doubt that the foramina in the roof of the fourth ventricle are true openings and not artefacts. The central one is the foramen of Magendie and the lateral openings bear the name of Luschka. Through these channels the fluid passes into the subarachnoid space and reaches the large *cisterna magna* dilatation (*cisterna magna*) which is situated at the medial cerebello-bulbar angle. From this *cisterna* the fluid passes slowly down the spinal canal with the arachnoid membrane and then, with some loss due to absorption and some gain due to formation in the cells lining the channel it returns to the cerebral subarachnoid space. The circulation upwards from the *cisterna magna* is somewhat more rapid and the fluid bathes the base of the brain, the cerebral hemispheres, and indeed the whole central nervous system (see fig. 387).

Absorption

When a readily diffusible dye is introduced into the subarachnoid space its rapid appearance in the blood of the venous sinuses under certain conditions demonstrates a possible path of absorption of the fluid. When the dye is injected into the cisterna magna and the spinal canal is blocked the absorption is not significantly lessened. This indicates that the fluid is largely absorbed from the cranial subarachnoid spaces. Key and Retzius believed that the fluid was absorbed through the Pacchionian granulations but these are absent from the brains of infants and are now regarded as pathological enlargements of a few of the arachnoid villi. By long-continued slow injection of an isotonic solution of a mixture of potassium ferrocyanide and iron ammonium citrate, Weed was able to demonstrate that the particles of Prussian-blue formed when the tissue was subsequently fixed in acid medium, precipitated in the mesothelial cells of the tips of the arachnoid villi and within the dural sinuses into which these villi project. A relatively slow absorption by way of the perineural spaces into the lymphatic system was also demonstrated. These findings have been confirmed and it may be accepted that the main absorption of the cerebrospinal fluid is through the arachnoid villi into the great venous sinuses. The pathway postulated by Key and Retzius has therefore been established but the numerous microscopic arachnoid villi have been substituted for the Pacchionian granulations.

MECHANISM OF ABSORPTION. Since the hydrostatic pressure in the subarachnoid space is always greater than that in the dural sinuses filtration is apparently adequate to account for the flow of fluid into the venous blood stream. True solutions readily pass through the arachnoid villi, colloids more slowly, the rate depending upon the size of the molecule; particulate matter does not pass. No evidence of any secretory activity of the arachnoid villi has been obtained.

Composition and mechanism of formation

In table 82 the amounts of the components of the cerebrospinal fluid are compared with those of blood plasma. The values given were obtained from analyses of lumbar fluid, that obtained from the ventricles may be slightly different. The water content of a unit weight of spinal fluid is somewhat greater than that of blood. The question arises, how is the fluid formed? It will be apparent from the table that if certain

constituents are investigated, diffusion from the blood plasma will be sufficient to account for the findings. However, before a decision can be reached as to whether the process is one of simple diffusion or of secretion, the concentrations of all the substances on both sides of the semipermeable membrane (the chorioid plexus) must be determined. This was done by Flexner whose findings indicate that work must be done to form this fluid, i.e., that it is not merely a filtrate from blood plasma. Since the hydrostatic pressure of the capillary blood is believed to be greater than that of the spinal fluid, except under grossly abnormal

TABLE 82*
Comparisons of amounts of main constituents of blood plasma and cerebrospinal fluid

	BLOOD PLASMA	CEREBROSPINAL FLUID
	mgm. per 100 cc.	mgm. per 100 cc.
Protein.....	6300-8500	16-38
Amino acids.....	4.5-9	1.5-3
Creatinine.....	0.7-2.0	0.45-2.20
Uric acid.....	2.9-6.9	0.5-2.8
Cholesterol.....	100-150	absent
Urea.....	20-42	5-39
Sugar.....	70-120	45-80
Chloride (NaCl).....	560-630	720-750
Inorganic phosphate.....	2-5	1.25-2.0
Bicarbonate (volumes per cent CO ₂).....	40-60	40-60
Hydrogen ions (pH).....	7.35-7.40	7.35-7.40
Sodium.....	325	325
Potassium.....	20	12-17
Magnesium.....	1-3	3-3.6
Calcium.....	9.0-11.5	4.0-7.0
Lactic acid.....	10-32	8-27

* Data largely that compiled by Flexner.

conditions, this factor and the secretory power of the cells of the plexus are the two forces to be considered. Thermodynamic considerations indicate that the hydrostatic pressure difference would provide only a small fraction (about one-thirteenth) of the energy necessary. This leads to the conclusion that ultrafiltration will not account for the formation of the cerebrospinal fluid and that the cells of the chorioid plexus perform work during this process.

The amount and pressure

Accurate figures for the volume of the fluid in the various age groups are not available. The methods used to investigate the problem involve a

change of conditions which invalidate the results secured. The total volume in healthy adults has been given as approximately 130 cc. The normal rate of formation has not been established. When artificial drainage is provided very large volumes, several liters per day, may drain away. The results of the urinary excretion of dye injected into the cerebrospinal space suggest that the volume of fluid is renewed every three or four hours but this rate of formation is probably too high. In recent experiments in which precautions were taken to interfere as little as possible with normal pressure



FIG. 387. Lateral, horizontal view of the ventricular system. A, intraventricular foramina; B, foramen of Monro; C, anterior commissure; E, posterior commissure; F, pineal gland; G, aqueduct of Sylvius; H, fourth ventricle; I, (darker shadow) lateral recesses superimposed on the shadow of the fourth ventricle; J, superior posterior recess of the fourth ventricle; K, foramen of Magendie; L, tonsils of cerebellum; M, pons; N, medulla oblongata; O, anterior medullary velum; P, lingula of vermis of cerebellum; Q, posterior medullary velum; R, nodulus of vermis of cerebellum; S, lamina terminalis; T, choroid plexus and ependyma of roof of third ventricle; U, fornix; V, suprapineal recess (from Davidoff and Dyke).

conditions, Flexner and Winters found in experiments with adult cats, that approximately 12 cc. of fluid per day could be collected from a cannula fixed in the aqueduct. The pressure of the cerebrospinal fluid may be taken as 110 to 130 mm. of Ringer's for man in the recumbent position. Fluid drops at the rate of approximately one drop per second from the lumbar puncture needle. Pressure on the internal jugular vein or the rise of venous pressure produced by crying or coughing causes an increase in pressure of the fluid presumably by increasing the size of the capillary bed in the brain. If the rise in venous pressure is long maintained

there may also be retardation of the absorptive fluid.

EFFECT OF FLUID AND SALT INJECTIONS PRESSURE (WEED AND HUGHSON). When large volumes of isotonic solutions are injected intravenously there is a transient rise in venous cerebrospinal pressure. Hypotonic solutions cause a prolonged rise in fluid pressure due presumably to the passage of fluid into the brain. There is a marked and more transient rise of venous pressure.

Hypertonic solutions (30 per cent NaCl) administered intravenously, produce a fall in cerebrospinal pressure which may persist for long periods. Fluid is apparently attracted by the raised osmotic pressure of the blood from the brain substance, perivascular spaces, etc., into the blood stream. There is evidence also (Foley) that the direction of flow of the cerebrospinal fluid may be reversed. When the aqueduct of Sylvius is obstructed and intraventricular pressure is measured during injection of the hypertonic solution, a fall in pressure within the ventricles is noted. Using Weed's Prussian-blue, Foley was able to show that the dye passed from the ventricles into the capillaries of the choroid plexuses. When the aqueduct is open there is a current of fluid from the subarachnoid space into the ventricles. The phenomena are attributable to the raised osmotic pressure in the capillaries of the choroid plexuses.

Weed and Hughson's work was soon applied to the clinic. Intravenous injection of hypertonic saline has greatly facilitated brain operations by causing shrinkage of the brain and thus preventing extrusion of brain substance through trephine openings. It is obvious also that raised intracranial pressure resulting from various causes may be favorably affected, for a time at least, by the withdrawal of fluid from the brain. The raised osmotic pressure of the blood is usually produced by intravenous administration of saline but the oral route may be used (Cushing).

EFFECT OF CHANGE OF POSITION ON PRESSURE. It is important to realize that the fluid in the subarachnoid space of the brain and spinal cord may be regarded as a single column (approximately 60 mm. long in the man of medium height). There are no structures to act as valves and restrictions of flow are not sufficient appreciably to interfere with this relationship. The change in pressure produced by a change of position can largely be predicted by hydrostatic considerations when the blood pressure remains constant, but the elasticity of the dural sac varies in different individuals. The pressures in the lumbar and occipital regions are

entical when the subject is horizontal. The pressure in the lumbar region in man is approximately 10 mm. higher in the sitting than in the prone position. The pressure in the human cisterna magna in the erect posture is probably below atmospheric. Experimental data indicate that some point in mid-thoracic region has a pressure coinciding with that of the atmosphere. The further exploration of these questions gives promise of important advances in our knowledge of the hydrostatics of the cerebrospinal fluid (Weed). The hypothesis formulated by Monro and supported by Kellie (the Monro-Kellie doctrine) postulated constancy of cerebral volume, i.e., a reciprocal relationship between the volumes of blood and spinal fluid. The third substance within the dural sac, the brain cells, are usually assumed to remain of constant volume. This hypothesis has been restated by Weed and now includes an "elastic" factor which takes into consideration a component depending on the ease of vascular adjustments as well as the distensibility and collapsibility of the meningeal sac.

Function of the cerebrospinal fluid

The fluid within the elastic meningeal sac serves as a protective covering for the nerve cells. By change in its volume compensation for change in the amount of blood is effected and the contents of the cranium thus tend to remain of constant volume. There is probably considerable exchange of metabolic materials between the nerve cells and the fluid.

Ventriculograms and Encephalograms

The location of a bubble of air injected into the cerebral ventricles (encephalogram) or through a lumbar puncture can be detected by X-ray. The air should rise to the top of the column of fluid and follow change in position of the subject. Failure

to do this suggests abnormality of the communicating channels.

Lipiodol, an iodized vegetable oil, opaque to X-rays, is sometimes injected into the cisterna magna. Normally it falls to the lower region of the spinal canal but narrowing of the canal by tumor or adhesions may prevent its passage and the level of the obstruction can in this way be determined from X-ray pictures.

Hydrocephalus

A consideration of the formation, circulation and absorption of the spinal fluid leads to the assumption that hydrocephalus might be produced by (1) Increased rate of formation of fluid. A very definite increase can be produced by the administration of hypotonic solutions (Weed) but the decreased tonicity of the blood cannot be maintained long enough to permit the development of hydrocephalus. Clinically hypertrophy of the choroid plexuses might produce this condition and a suggestive case has been reported (Davis). (2) Obstruction to the passage of the fluid. An obstruction by tumor or inflammation in the right foramen of Monro, for example, would produce a right internal hydrocephalus. Blockage of the aqueduct of Sylvius would produce a bilateral internal hydrocephalus as would an obstruction in the fourth ventricle or at the foramina of Magendie and Luschka. (3) Interference with the absorption of fluid by way of the arachnoid villi. Blockage of many of these villi or interference with their function by other means may lead to an external hydrocephalus. Increased intracerebral venous pressure might produce a temporary decrease in absorption of fluid or, as Cushing has suggested, venous sinus thrombosis if this were compatible with life.

CHAPTER LXXIII

THE AUTONOMIC NERVOUS SYSTEM

(Synonyms—involuntary nervous system, vegetative nervous system)

The autonomic nervous system has been touched upon in many of its aspects in other sections of this book. There remains to be given an account of the structural plan of this system as a whole, a general summary of its functions and of the structures which it innervates. From anatomical, physiological and pharmacological viewpoints the autonomic system falls naturally into two main divisions—the *sympathetic* or *thoracolumbar outflow* and the *parasympathetic* or *craniosacral outflow* (see fig. 388).

THE SYMPATHETIC DIVISION

The cells of origin of the sympathetic division are situated in the lateral horns of the spinal cord (intermediolateral cell column) from the 8th cervical or 1st thoracic to the 2nd or 3rd lumbar segments. The axons of these cells leave the cord by the corresponding anterior nerve roots and connect with nerve cells in one or other of the outlying ganglia. The fibers arising from the spinal cells are medullated and are called *preganglionic*; those arising from cells of the ganglia are non-medullated, and are called *postganglionic*. Evidence for the existence of a higher center in the posterior region of the hypothalamus has been considered in Chapter LXVIII.

The ganglia are arranged in three systems or groups: (A) *vertebral* (or *central*), (B) *prevertebral* (or *collateral*) and (C) *terminal* (or *peripheral*).

A. THE VERTEBRAL GANGLIA AND GANGLIATED CORD

The vertebral group of ganglia lies in close relation to the vertebral bodies and consists, on each side, of a series of some 22 ganglia connected together by intervening fiber tracts to form a nodular cord extending from the base of the skull to the front of the coccyx. This is known as the *sympathetic chain* or the *gangliated cord of the sympathetic*. It will be described in sections.

The cervical part of the sympathetic chain

The cervical part of the sympathetic chain possesses three ganglia—the *superior*, *middle*

and *inferior cervical ganglia*. They are relatively large and are believed to result from the fusion of two or more smaller ganglia.

THE SUPERIOR CERVICAL GANGLION, situated below the base of the skull, is the largest of the three; the sympathetic supply to the head is derived from cells contained within it; it is probably formed by the fusion of the upper four cervical ganglia. Its branches are:

(1) THE INTERNAL CAROTID NERVE. This arises from the upper pole of the superior cervical ganglion and, passing into the cranium with the artery of the same name, forms the internal carotid and cavernous plexuses.

The *Internal Carotid Plexus*, situated on the lateral side of the internal carotid artery sends branches the following:

(a) The abducent nerve.

(b) The tympanic branch of the glossopharyngeal nerve.

(c) The sphenopalatine ganglion by way of the deep petrosal and the great superficial petrosal nerve which join to form the nerve to the pterygoid canal (Vidian nerve). Orbital branches of the sphenopalatine ganglion convey sympathetic fibers to the lacrimal gland; the soft palate, nasopharynx and pharynx receive fibers through the palatine and pharyngeal branches of the ganglion.

(d) The semilunar ganglion.

The sympathetic fibers pass through the sphenopalatine and semilunar ganglia without interruption.

The *Cavernous Plexus*, situated on the inner side of the internal carotid artery as it lies in the cavernous sinus, sends branches to the following:

(a) The oculomotor, trochlear and abducent nerves and the nasociliary branch of the ophthalmic division of the trigeminal nerve. Through the long ciliary nerves (twigs of the nasociliary nerve), sympathetic fibers are conveyed to the dilator pupillae (see also p. 1013).

(b) The ciliary ganglion, through which the sympathetic fibers pass without interruption into the short ciliary nerves. These fibers provide an additional pathway for sympathetic impulses to the dilator of the pupil.

(c) The pituitary body.

Through the communicating branches of the cavernous plexus the vessels of the eyeball and nasal mucosa are supplied with constrictor fibers, and the skin of the nose with vasoconstrictor, motor (smooth muscle) and secretory (sweat) fibers. The terminal filament

the internal carotid and cavernous plexuses are continued as delicate networks over the anterior and middle cerebral arteries to the minute vessels of the pia mater, and along the ophthalmic artery to the structures of the orbit.

(2) Branches to the UPPER FOUR CERVICAL NERVES.

(3) Twigs to the GANGLION JUGULARE AND GANGLION NODOSUM OF THE VAGUS, to the PETROUS GANG-

branches of the external carotid and supplies fibers to the vessels, sweat glands and cutaneous muscles of the face. Filaments from the plexus investing the facial artery pass to the submaxillary ganglion. The plexus on the middle meningeal artery sends fibers to the otic ganglion; these pass without interruption into the auriculotemporal nerve through which they reach the parotid gland.

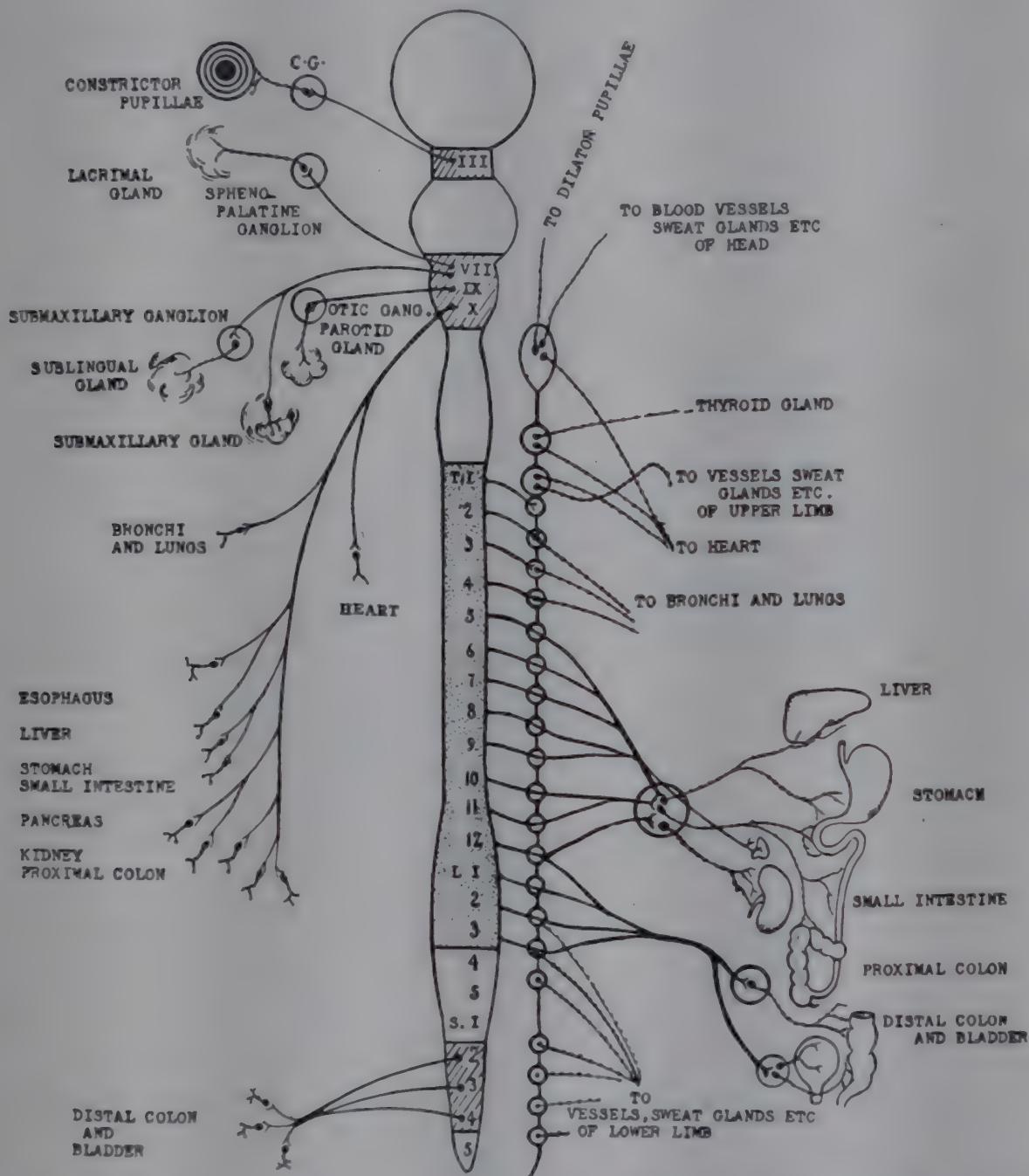


FIG. 388. Showing plan of autonomic nervous system. C.G., ciliary ganglion. The celiac, inferior mesenteric and hypogastric ganglia are represented, in this order from above downwards, by the circles in the lower right portion of the diagram.

LION OF THE GLOSSOPHARYNGEAL NERVE and to the HYPOGLOSSAL NERVE.

(4) Filaments to the CAROTID SINUS and CAROTID BODY.

(5) The SUPERIOR CARDIAC NERVE to the cardiac plexuses.

(6) Branches which ramify in a plexiform manner upon the external carotid artery—the EXTERNAL CAROTID PLEXUS. This plexus is continued over the

THE MIDDLE CERVICAL GANGLION is formed presumably by the coalescence of the fifth and sixth cervical ganglia. Its branches are as follows:

(1) Branches to the *fifth and sixth cervical nerves* and thence to the blood vessels, sweat glands and cutaneous muscle within the area of distribution of these nerves.

- (2) *The middle cardiac nerve* to cardiac plexuses.
- (3) Branches which extend along the inferior thyroid artery to the *thyroid gland*.

THE INFERIOR CERVICAL GANGLION probably represents the union of the seventh and eighth cervical ganglia; it may be fused with the first thoracic ganglion. It gives off the following branches:

- (1) Branches to the *seventh and eighth cervical nerves*.
- (2) *The inferior cardiac nerve* to cardiac plexuses.
- (3) Branches which form plexuses upon the subclavian artery and its branches. Sympathetic fibers are thus carried into the cranial cavity along the vertebral artery, and over the axillary and commencement of the brachial (see also p. 232).

The thoracic, lumbar and sacral portions of the gangliated cord

The *thoracic ganglia* are 10 or 12 in number on each side. They are evenly spaced, one to each spinal segment. In the dog and cat, and in many human subjects, the first thoracic and inferior cervical ganglia are partially or completely fused to form an irregularly shaped mass, called the *stellate ganglion*. There are usually 4 *lumbar* and 4 or 5 *sacral* ganglia. The sacral portions of the two sympathetic trunks converge below and fuse upon the anterior surface of the coccyx to form a terminal swelling—the *coccygeal ganglion* or *ganglion impar*.

B. THE PREVERTEBRAL GANGLIA

These lie in the thorax abdomen and pelvis in relation to the aorta and its branches. The larger of the prevertebral ganglia are: (a) the *celiac (solar or semilunar) ganglion*, lying in relation to the origin of the celiac artery, (b) the *superior mesenteric ganglion*, situated below the origin of the superior mesenteric artery, and (c) the *inferior mesenteric ganglion*, which bears a corresponding relation to the inferior mesenteric artery; this ganglion is rarely present in man (see also p. 940).

C. THE TERMINAL GANGLIA

These consist of small collections of ganglion cells situated in close relation to the innervated organs, especially those of the pelvis, e.g., the bladder and rectum.

THE OUTFLOW OF SYMPATHETIC FIBERS FROM THE CENTRAL NERVOUS SYSTEM

It has already been pointed out that the cell giving rise to the sympathetic fibers (p. 936) is situated in the thoracic and upper lumbar segment of the cord. It is from this limited region (8th C. or 1st T. to 2nd or 3rd L. inclusive) that the sympathetic (preganglionic) fibers emerge. *This region constitutes the only outlet for sympathetic impulses.* So the term thoracolumbar outflow simply means the sympathetic division of the autonomic nervous system. The fibers emerge from the cord through the anterior root of the spinal segment in which their cell bodies are placed. In a cross section of the anterior root they appear as fine medullated fibers (2.5μ or less in diameter) intermingled with the larger, medullated, somatic (motor) fibers. They separate almost immediately, however, from the voluntary motor fibers of the anterior root and enter the corresponding ganglion of the sympathetic chain. Thus, the spinal nerves from the 8th cervical or 1st thoracic to the 2nd or 3rd lumbar, but not others, are connected each to a vertebral ganglion by a delicate white strand composed of preganglionic fibers and known as the *white ramus communicans* (plural *rami communicantes*, fig. 389 and fig. 102, p. 233). A preganglionic fiber after entering the ganglion may pursue one of three courses: (a) form synapses with cells in the ganglion which it first enters, (b) pass up or down the sympathetic trunk for some distance to terminate in a ganglion at a level higher or lower than that of the segment from which it originated. It may give off collateral branches to ganglion cells along its course. In any event, the preganglionic fibers issuing from a given segment connect with several ganglia (from five to nine). Furthermore, each preganglionic fiber may form a large number of synapses within a given ganglion. Ranson and Billingsley found that in the case of the superior cervical ganglion each fiber communicated with some twenty-two ganglion cells; this accounts for the diffuse nature of the sympathetic discharge. (c) Traverse the gangliated cord without interruption to find a cell station in either a prevertebral or a terminal ganglion.

PLAN OF DISTRIBUTION OF SYMPATHETIC FIBERS TO THE PERIPHERY

To the limbs and trunk

The ganglia of the sympathetic chain are connected with the spinal nerves supplying the

limbs and trunk by delicate filaments called *gray rami communicantes*. They are composed of the axons of the ganglion cells and are therefore called *postganglionic*. The gray rami in the thoracic and upper lumbar regions join the spinal nerves close to the points at which the white rami arise. Their constituent fibers are continued to the periphery for the supply of the blood vessels, sweat glands and smooth muscle of the skin. Whereas, as already mentioned, only a limited number of spinal nerves possess white rami,

the upper limb as well as those to the head and neck and heart. This operation may fail, however, completely to remove the sympathetic supply to the arm since a gray ramus (Kuntz's nerve) frequently passes from the second thoracic ganglion via the first thoracic nerve to join the brachial plexus.

To the head and neck

Sympathetic impulses to the structures of the neck, face, scalp and intracranial cavity are con-

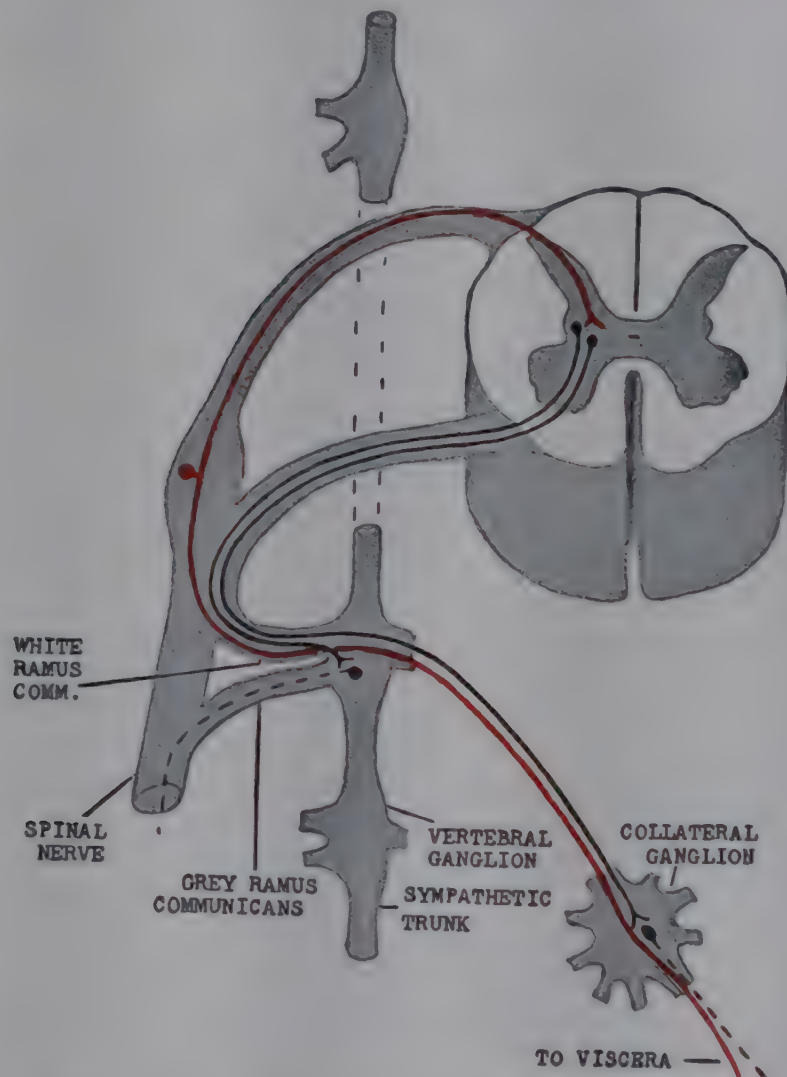


FIG. 389. Diagram showing the connections of sympathetic fibers. Efferent fibers in black; preganglionic, solid lines; postganglionic, interrupted lines. Afferent visceral fiber in red.

every spinal nerve receives a gray ramus. It therefore follows that sympathetic impulses going to parts supplied by upper cervical, lower lumbar or sacral somatic nerves, must travel considerable distances up or down the sympathetic trunk before reaching an outlet through a gray ramus. The postganglionic fibers to the upper limb arise from the first thoracic, and the inferior and middle cervical ganglia; those for the lower limb from the lumbar and sacral ganglia. Excision of the stellate ganglion (inferior cervical and first thoracic) interrupts the sympathetic pathways to

veyed from the cord in the white rami of the upper two thoracic nerves. They ascend to connect with cells in the middle and superior cervical ganglia. From the latter postganglionic fibers are distributed through the internal carotid, cavernous and external carotid plexuses as described on page 936. The sympathetic as well as supplying the blood vessels, sweat glands and pilomotor muscles of the head and neck also innervates the salivary glands, the dilator pupillae, Mueller's muscle and the smooth muscle component of the levator palpebrae superioris. Sympathetic fibers

also descend the infundibular stalk to the pituitary gland. The spinal center for the dilator pupillae is situated (in man) in the 8th cervical segment.

To the thoracic viscera

The sympathetic postganglionic fibers join with the branches from the vagus to form the *cardiac*, *pulmonary* and *esophageal plexuses*.

The *cardiac plexus* lies in relation to the origins of the aorta and pulmonary artery. It consists of a superficial and a deep portion, and is formed by the interlacement of fibers from the cardiac branches of the vagus (parasympathetic) and sympathetic nerves. The vagus fibers are preganglionic. They terminate around ganglion cells in the walls of the heart (p. 205). The sympathetic fibers derived from the superior, middle and inferior cardiac nerves are postganglionic, their cell stations lying in the corresponding cervical ganglia (fig. 95, p. 207). The preganglionic fibers arise from the upper four or five thoracic segments of the cord.

The *pulmonary plexuses*, anterior and posterior, lie in relation to the corresponding aspects of the root of the lung. They are formed from postganglionic fibers of the sympathetic (T. 2, 3 and 4) and preganglionic fibers of the vagus. The latter connect with ganglion cells in the walls of the bronchi. Herein is situated an intrinsic nervous plexus consisting of these ganglion cells and medullated and non-medullated fibers.

The *esophageal plexus* embraces the lower half of the esophagus. Vagal and sympathetic fibers (from the upper thoracic ganglia and from the thoracic portion of the great splanchnic nerve) enter into its formation. The vagal fibers end around ganglion cells of the intrinsic plexus of Auerbach in the esophageal wall.

To the abdominal and pelvic viscera

The *greater, lesser and least splanchnic nerves*. These are composed of preganglionic fibers, and may be looked upon as elongated white rami. They connect with cells in the prevertebral (collateral) ganglia. The postganglionic fibers after emerging from the latter join the neighboring plexuses. The *greater splanchnic* nerve arises from the cord from as high as the 4th or 5th thoracic segment, and as low as the 9th or 10th. Its fibers end in the upper part of the celiac ganglion; from here postganglionic fibers are continued into the celiac plexus. The *lesser splanchnic* and the *least (or lowest) splanchnic* nerves are much smaller.

The former arises from the 10th and 11th thoracic segments and its fibers, after passing without interruption through the vertebral ganglia at these levels, end in the lower portion of the celiac ganglion. The least splanchnic nerve arises from the last one or two thoracic segments and first lumbar segment; it joins the renal plexus (fig. 390).

The *lumbar splanchnic nerves* are three or four strands which arise from the second and third lumbar segments. Their fibers pass through the lumbar portion of the sympathetic chain and enter the inferior mesenteric ganglion; here some are relayed, others are continued without interruption and find their cell stations in peripheral ganglia.

THE PLEXUSES OF THE ABDOMEN AND PELVIS. The sympathetic fibers form rich plexuses in relation to the aorta and its branches from which filaments pass to the abdominal and pelvic viscera. Parasympathetic fibers also enter into the constitution of these plexuses.

The *celiac (or solar) plexus* lies upon the abdominal aorta at the origin of the celiac artery. The *celiac ganglia*, right and left, lie embedded within the plexus, which is made up of fibers arising in the ganglion (i.e., postganglionic fibers of the greater and lesser splanchnic nerves) together with preganglionic fibers of the vagus. The lower part of the celiac ganglion is often detached and is then referred to as the *aorticorenal ganglion*. The plexus invests the celiac artery throughout its course and gives rise to several subordinate plexuses—the *hepatic, gastric, splenic, renal* and *adrenal plexuses*—which invest the corresponding arteries and their branches.

The *superior mesenteric plexus* is continuous above with the celiac plexus. It surrounds the superior mesenteric artery, along the branches of which it is prolonged. The plexus is composed of postganglionic fibers which arise in an aggregation of nerve cells—the *superior mesenteric ganglion*—lying within it, and of preganglionic fibers derived from the lumbar segments of the cord. The superior mesenteric plexus supplies the pancreas, and the small intestine and the large intestines as far as the commencement of the descending colon.

The *aortic or intermesenteric plexus* lies upon the aorta between the origins of the superior and inferior mesenteric arteries. It receives fibers from the celiac plexus and from the upper lumbar ganglia. The aortic plexus gives rise secondarily to the *spermatic* and *ovarian plexuses* which supply the testes and ovary with autonomic fibers. It is connected below with the *inferior mesenteric plexus* which invests the artery of the same name. The *inferior mesenteric ganglion*, a collection of ganglion cells lying within the latter plexus, receives the lumbar splanchnics; this ganglion is not present,

as a rule, in the human subject (Learmonth). The plexus is formed of fibers derived from the aortic plexus and from the inferior mesenteric ganglion when this is present. From it secondary plexuses arise which invest the branches of the inferior mesenteric artery and carry sympathetic impulses to the descending colon, iliac colon, pelvic colon and rectum.

among which are scattered numerous small ganglia which are sometimes referred to collectively as the *hypogastric ganglion*. Parasympathetic fibers enter the inferior hypogastric plexuses through the pelvic nerve (sacral outflow, p. 842). The sympathetic fibers contributing to the pelvic plexuses have their ultimate source in the lumbar segments of the cord.

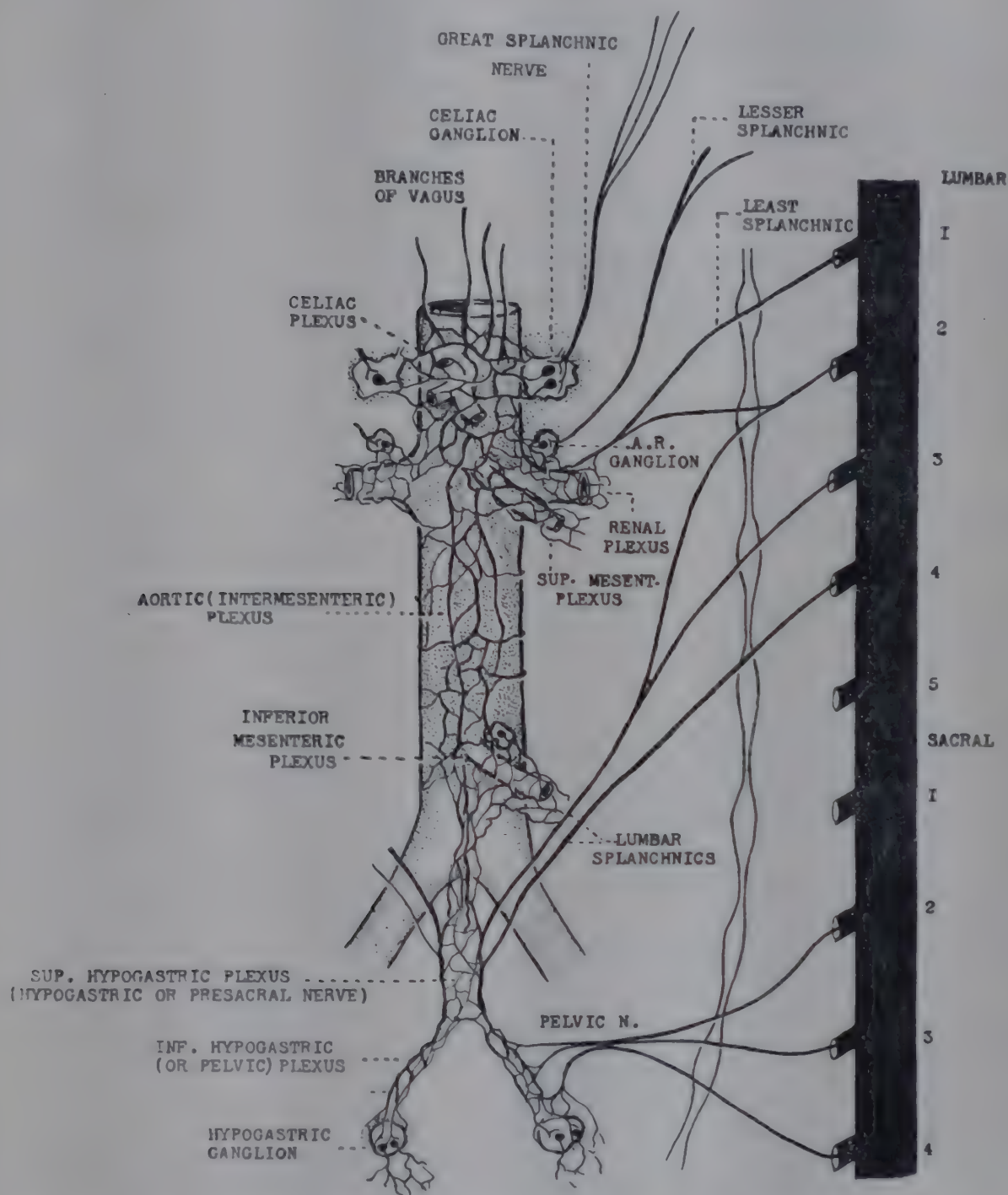


FIG. 390. Diagram of the nerve plexuses of the abdomen and pelvis. A.R., aortico-renal.

The *superior hypogastric plexus* is the downward extension of the aortic plexus. It lies in the angle formed by the bifurcation of the aorta. Though rarely condensed into a single bundle it is sometimes referred to as the *hypogastric nerve* or the *presacral nerve*. It transmits inhibitory impulses to the pelvic colon and via the pelvic plexuses to the rectum, bladder and other pelvic viscera. It divides below into the right and left *pelvic* or *inferior hypogastric plexuses*. These lie one on either side of the rectum and are composed of medullated and non-medullated fibers

They reach the plexuses via the hypogastric plexuses as well as more directly from the sacral part of the sympathetic chain. Through subsidiary plexuses—*hemorrhoidal, vesical, uterine, vaginal* and *prostatic*—fibers (sympathetic and parasympathetic) are conveyed from the pelvic plexuses to the pelvic viscera.

THE PARASYMPATHETIC OR CRANIOSACRAL DIVISION

The cells giving rise to parasympathetic fibers are situated at three different levels of the central nervous system—the *mid-brain*, the *medulla*

and the *sacral region of the spinal cord*. The axons of these cells leave the central nervous system to connect with ganglion cells lying within or in close relation to the innervated organ (see fig. 388). As in the case of the sympathetic division the axons of the central cells are called *preganglionic*; those of the ganglion cells, *postganglionic*. The former are medullated, the latter non-medullated.

The three levels from which parasympathetic fibers emerge will be referred to as the *tectal* (or *mid-brain*), the *bulbar* and the *sacral* outflows, respectively.

A. THE TECTAL OR MID-BRAIN OUTFLOW

The group of cells composing the Edinger-Westphal nucleus of the oculomotor nerve (p. 1016) are believed to give rise to the tectal fibers.

The autonomic fibers are conveyed in the third nerve as far as the ciliary ganglion where they find their cell stations. Postganglionic fibers emerge from the ganglion in the short ciliary nerves, and terminate in the sphincter pupillae and the ciliary muscle (p. 1012).

B. THE BULBAR OUTFLOW

These fibers leave the brain in the *facial*, *glossopharyngeal* and *vagus nerves*.

(1) The parasympathetic fibers (secretory and vasodilator) entering the *facial nerve* arise from the *superior salivary nucleus*, which lies dorsal and lateral to the lower end of the motor nucleus of the facial. These fibers emerge from the brain in the sensory root of the facial nerve (*nervus intermedius*, p. 859) and travel with the latter to the facial canal of the temporal bone. Here they leave the facial, (i) in its *chorda tympani* branch which later joins the lingual to be conveyed to the floor of the mouth. At this point some of the chorda fibers (secretory and vasodilator in function) separate from the lingual again to enter the submaxillary gland where they synapse with ganglion cells; other secretory and vasodilator fibers of the chorda tympani nerve proceed to the *submaxillary ganglion* from which postganglionic fibers pass to the sublingual gland (p. 417); (ii) in the great superficial petrosal nerve and nerve of the pterygoid canal (Vidian nerve) to the sphenopalatine ganglion. From here postganglionic fibers pass via orbital branches of the ganglion to the lacrymal gland, and to the mucous membrane of the soft palate, nasopharynx and pharynx via the palatine nerves.

(2) The parasympathetic fibers (secretory and vasodilator) of the *glossopharyngeal nerve* arise from cells of the *inferior salivary nucleus*. This nucleus lies below the superior salivary nucleus, and lateral to the motor nucleus of the glossopharyngeal nerve. The autonomic fibers leave the brain with the latter nerve but separate

from it again in its tympanic branch. The latter joins a branch of the genicular ganglion of the facial to form the small superficial petrosal nerve; the parasympathetic fibers are continued in the small superficial petrosal nerve to the otic ganglion from where postganglionic fibers are conveyed to the parotid gland via the auriculotemporal nerve (fig. 183, p. 418).

(3) The *vagus nerve* contains the greater proportion of the fibers of the bulbar outflow. They arise from the *dorsal nucleus* of the vagus and are distributed through the latter's numerous branches to the thoracic and abdominal viscera (p. 861). Unlike those in the other two cranial nerves, the preganglionic fibers of the vagus connect with ganglion cells situated within the innervated organs. Thus the vagal fibers to the heart connect with ganglion cells in the cardiac wall; those to the bronchi with the nerve cells of the intrinsic plexus in the bronchial walls; those to the esophagus, stomach and intestine form synapses with the ganglion cells of the myenteric plexus of Auerbach and the submucous plexus of Meissner. The preganglionic fibers are therefore quite long, the postganglionic very short.

C. THE SACRAL OUTFLOW

The cells of origin lie in the anterior horns of the 2nd, 3rd and 4th and sometimes the 1st sacral segments of the cord. The preganglionic fibers emerge in the anterior roots of the corresponding sacral nerves. The fibers leave the spinal nerves again and, proceeding peripherally as the *pelvic nerve* (or *nervus erigens*), on each side, enter into the formation of the pelvic plexus (p. 941). The fibers terminate around ganglion cells lying in close relation to the pelvic organs. They carry motor impulses to the walls of the descending colon, rectum and bladder; inhibitory impulses to the internal anal and vesical sphincters and to the uterus; and dilator impulses to the blood vessels of the bladder, rectum and genitalia.

THE AFFERENT VISCERAL NERVES

Impulses are transmitted from the viscera by afferent fibers which pass through the various plexuses and reach the central nervous system via the vagus, pelvic, splanchnics and other autonomic nerves. The *afferent fibers of the vagus* are the peripheral processes of cells in the ganglion jugulare and the ganglion nodosum. The central processes of these neurons terminate in the dorsal nucleus of the vagus (p. 861). Therein connections are made with efferent parasympathetic neurons to complete the reflex arc. The *afferent fibers of the pelvic nerve* arise from cells in the posterior root ganglia of the 2nd, 3rd and 4th sacral nerves. They pass peripherally with the

fferent autonomic fibers. The *afferent fibers of the sympathetic division* are the peripheral processes of ganglion cells in the posterior spinal nerve roots from the 1st thoracic to the 3rd lumbar segments. *None arise from sympathetic ganglia.* They reach the sympathetic trunk via the white rami communicantes and are distributed to the viscera along with the corresponding efferent fibers (fig. 389). Though some of these afferent fibers are non-medullated the majority are medullated, and of larger size than the efferent fibers. The ganglion cells of the posterior roots which give origin to the afferent fibers of the sympathetic (or of the pelvic nerve) have not been shown definitely to differ from those giving rise to the ordinary somatic sensory fibers. For this reason the sympathetic system proper is regarded as consisting solely of efferent neurons. The afferent fibers pass to their destinations without interruption in any of the sympathetic ganglia, passing directly to the viscera in the splanchnics or other visceral efferents. A certain proportion also enter the spinal nerves for distribution to the limbs via the gray rami.

The visceral reflex arc

The visceral reflex arc, as pointed out by Gaskell, is formed upon a plan similar to that upon which somatic reflexes are based. The afferent fiber in the latter instance is connected to the anterior horn cell through the intermediary of an intraspinal neuron or a series of such neurons. These are spoken of as connector neurons. In the case of visceral reflexes, the afferent fiber makes contact with a cell in the lateral horn of gray matter. The axon of this cell—the preganglionic fiber—which connects with a ganglion cell of the sympathetic system, corresponds to the connector fiber of the somatic reflex arc. In development, however, this neuron has migrated from the central nervous system, being only in part intraspinal. The neuron with which it communicates, i.e., the ganglion cell and postganglionic fiber, though it has been carried entirely beyond the bounds of the central nervous system, corresponds to the motor neuron of the somatic reflex arc.

A certain degree of independent reflex activity can be carried out through the intrinsic plexuses, e.g., of the intestine, when these are separated from the central nervous system by division of the main autonomic nerves. It is also true that some independent activity can be carried out through axon reflexes or possibly through some of the more peripherally placed ganglion cells. Other parts of the autonomic system, however,

cannot function apart from the central nervous system. The larger ganglia of the parasympathetic or sympathetic, for instance, do not serve as reflex centers. It is clear from the description of the origin and course of the visceral afferent nerves given above that no anatomical basis for such action exists.

THE FUNCTIONS OF THE AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system governs the activities of cardiac and smooth muscle, of the digestive glands and sweat glands, and of certain endocrine organs. It is concerned with those processes which normally are beyond voluntary control and are for the most part beneath consciousness. The term autonomic as applied to the system is not altogether suitable since, as we have seen, it is under the control of centers within the central nervous system, and cannot function as an independent unit.

Through its various activities the autonomic system exercises the important function of maintaining the constancy of the fluid environment of the body's cells; it serves to combat forces, acting either from within or without, which tend to cause variations in this environment. Regulation of the composition of the body fluids, of their temperature, quantity and distribution is effected through the actions of the autonomic nerves upon circulatory, respiratory, excretory and glandular organs. For example, of glandular structures under autonomic influence, the liver, pancreas and adrenal are of especial importance in the regulation of blood sugar; the sweat glands aid in the control of body temperature. The pituitary gland in some of its functions, at least, is also under autonomic control. The thyroid and probably the parathyroids are governed in turn by hormones liberated by the pituitary (p. 725); though it is not improbable that they may be influenced also by impulses received through autonomic paths. The stability of the internal environment (the *milieu interne* of Claude Bernard) which is so characteristic of the healthy body, is spoken of by Cannon as *homeostasis*. According to Cannon, the essential and particular function of the autonomic system is to bring about the internal adjustments upon which this constant state depends. He therefore refers to the autonomic nerves as the *interofective* system. He speaks of the voluntary system (i.e., the central nervous system and the somatic nerves) as the *exteroffective* system, since through its exteroceptors and

TABLE 83

ORGAN	PARASYMPATHETIC EFFECTS*	ORIGIN OF SYMPATHETIC POSTGANGLIONIC FIBERS	SYMPATHETIC EFFECT
<i>Heart</i> (p. 205, 207)	Inhibition	Superior middle and inferior cervical ganglia	Acceleration
<i>Vessels:</i>			
Cutaneous (p. 232-234)	—	Various vertebral ganglia	Constriction
Muscular (p. 234)	—	Various vertebral ganglia	Dilatation, Const.
Coronary (p. 278)	Constriction	Cervical ganglia	Dilatation
Salivary glands (p. 417)	Dilatation	Superior cervical ganglion	Constriction
Buccal mucosa	—	Superior cervical ganglion	Dilatation
Pulmonary (p. 284)	Dilatation and constriction	Thoracic vertebral ganglia	Constriction and dilatation
Cerebral (p. 290)	Dilatation	Superior cervical ganglion	Constriction
Abdominal and pelvic viscera (p. 940)	—	Prevertebral ganglia	Constriction
External genitalia (p. 236)	Dilatation	Prevertebral ganglia	Constriction
<i>Eye:</i>			
Iris (p. 1012)	Constriction	Superior cervical ganglion	Dilatation
Ciliary muscle (p. 1016)	Contraction	Superior cervical ganglion	Relaxation
Smooth muscle of orbit and upper lid (p. 1016)	—	Superior cervical ganglion	Contraction
Nictitating membrane (cat and dog)	—	Superior cervical ganglion	Retraction
<i>Bronchi</i>	Constriction	Thoracic ganglia	Dilatation
<i>Glands:</i>			
Sweat (p. 939)	—	Vertebral ganglia	Secretion
Salivary (p. 417)	Secretion	Superior cervical ganglia	Secretion
Gastric (p. 430)	Secretion	Celiac ganglion	Inhibition?
Pancreas (p. 452)			Secretion of mucus
Acini	Secretion	Celiac ganglion	—
Islets	Secretion	Celiac ganglion	—
Liver (p. 592)	—	Celiac ganglion	Glycogenolysis
Adrenal (p. 684) medulla	—	No postganglionic fibers	Secretion
<i>Smooth muscle:</i>			
Of skin	—	Vertebral ganglia	Contraction
Of stomach wall (p. 488)	Contraction or inhibition	Celiac ganglion	Contraction or inhibition
Of small intestine (p. 501)	Increased tone and motility	Celiac and superior mesenteric ganglia	Inhibition
Of large intestine (p. 502)	Increased tone and motility	Inferior mesenteric and hypogastric ganglia	Inhibition
Of bladder wall (p. 413) (detrusor muscle)	Contraction	Inferior mesenteric and hypogastric ganglia	Inhibition
Of trigone and sphincter	Inhibition	Inferior mesenteric and hypogastric ganglia	Contraction
Of uterus, pregnant		Inferior mesenteric and hypogastric ganglia	Contraction
Of uterus, non-pregnant			Inhibition

* With certain exceptions, e.g., those supplying the sublingual and parotid glands and the sphincter pupillae the postganglionic fibers of the parasympathetic arise from cells situated in, or in close proximity to, the innervated organ itself.

effectors a direct relationship is established with the external environment.

The great majority of the effector organs of the autonomic system are innervated by both sym-

pathetic and parasympathetic divisions (see table 83), and the effects exerted by the two types of fiber going to a given organ are antagonistic. Thus the heart's action is inhibited by the vagus

but augmented by the sympathetic (p. 207). In the intestine the effects of the two nerves are reversed, the parasympathetic (vagus nerve to the small bowel, pelvic nerve to the large) is augmentor; the sympathetic inhibitory. The removal of the effects of one set of fibers, as by section, results, as a rule, in the effects of the other set becoming more prominent. This fact indicates that each type of fiber exerts a constant or tonic action and suggests that the two effects are delicately balanced one against the other. Thus, section of the vagus nerves causes an increase in the cardiac rate, and section of the parasympathetic or of the sympathetic fibers to the iris causes, respectively, dilatation or constriction of the pupil. See pupillary reactions, p. 1011.

Taken as a whole the actions of the sympathetic division and its ally the adrenal gland (sympathoadrenal system, p. 690) are directed towards strengthening an animal's defences against the various dangers which beset it, e.g., extremes of temperature, deprivation of water or the attacks of its enemies. It has been shown by Cannon, however, that the sympathetic system is not indispensable; both gangliated cords may be completely removed yet the animal remains in good health provided it is kept in the sheltered environment of the laboratory. Sympathectomized cats if kept warm and carefully tended will live indefinitely. Kittens deprived of their sympathetic trunks grow normally, female cats become pregnant and give birth to young, though the mammary glands do not function and the maternal instinct is lacking. Sympathectomized animals are, however, incapable of arduous work, sugar is not mobilized from the liver on demand, an increase of circulating red cells does not occur during excitement or exercise (p. 54), the usual reactions to cold (elevation of the hairs and vasoconstriction) fail, and adrenaline is not liberated in an emergency. They are also less able to withstand oxygen lack or hemorrhage than are normal animals. It is evident that the sympathectomized animal could not fend for itself, and, in the struggle for existence, would soon succumb to the hazards of the environment.

Parasympathetic effects, rather than being characterized by a diffuse outburst of activity, as may result from sympathetic stimulation, are more localized in character. It has also been suggested that they are concerned with conservative and restorative processes, and the sympathetic with processes involving the expenditure of energy.

Inhibition of the heart, contraction of the pupil for the protection of the eye from intense light and the activities of the digestive tract, through which the energy stores of the body are replenished, are frequently given as examples of acts of conservation presided over by the parasympathetic. These apparent differences in the activities of the two divisions have led some to speak of the functions of the sympathetic and parasympathetic divisions as *catabolic* and *anabolic*, respectively. It is an interesting but perhaps a too speculative generalization.

A summary of the actions of the autonomic system upon various structures is given in table 83.

THE ACTIONS OF CERTAIN DRUGS UPON THE AUTONOMIC SYSTEM

NICOTINE paralyzes ganglion cells or the junction (synapse) between the cell and the pre-ganglionic fiber. The fibers themselves remain unaffected by the drug. An excitatory effect precedes the paralysis. The power of nicotine to paralyze ganglion cells renders it a most valuable means of locating the ganglion cells of autonomic nerves. If, for example, after a certain ganglion has been painted with the drug, stimulation of the fibers on the proximal side of the ganglion fails to cause the customary response, then it is concluded that the fibers in question have their cell stations in the treated ganglion. Nicotine also causes the contraction of striated bird and frog muscle and of denervated mammalian muscle. This excitatory effect is abolished by an excess of nicotine.

ADRENALINE (p. 685) acts upon structures innervated by the sympathetic. The sweat glands of most animals are an exception. Denervation of the effector organ sensitizes it to the action of adrenaline (p. 947).

ERGOTOXINE AND ERGOTAMINE paralyze motor and secretory fibers of the sympathetic but not the inhibitory fibers. When injected intravenously into the conscious animal (cat) ergotoxine produces a condition of "sham rage" (p. 884).

PILOCARPINE causes parasympathetic effects, e.g., cardiac inhibition, contraction of the smooth muscle of the eye, bronchioles and alimentary tract, and secretion from the salivary, bronchial and gastric glands. *It also stimulates the sweat glands* which receive excitatory fibers from the sympathetic. The action of pilocarpine like that of muscarine or of acetylcholine is directly upon the effector cell.

MUSCARINE acts similarly to pilocarpine upon the heart and the smooth muscle of the alimentary tract, bladder and bronchioles. It constricts the pupil, and stimulates the salivary glands and sweat glands. It also causes vasodilatation.

CHOLINE AND ITS ESTER, ACETYLCHOLINE imitate closely the effects of parasympathetic stimulation, causing cardiac inhibition, excitation of the smooth muscle of the digestive tract and bladder wall, and the secretion of saliva, tears and sweat. It causes in addition dilatation of the arterioles and a fall in blood pressure. Acetylcholine is some 1000 times more powerful than choline itself. One part in many millions causes inhibition of the perfused frog's heart or contraction of an isolated intestinal segment. The ester is rapidly hydrolyzed in alkaline media into acetic acid and choline, and blood and other body fluids contain an enzyme—*cholinesterase*—which rapidly inactivates it. The action of the esterase is inhibited by physostigmine. This drug, therefore, by preventing the destruction of acetylcholine by the body fluids, greatly intensifies its action. In addition to the parasympathetic effects of acetylcholine, which have been termed its "muscarine" action, it has a stimulant action upon ganglion cells, upon the muscles of the body wall of the leech, upon voluntary frog muscle and upon denervated mammalian muscle. These effects of acetylcholine resemble those caused by nicotine and are referred to as its "nicotine" action. The latter, unlike the "muscarine" action, is not annulled by atropine but is abolished by a large dose of nicotine and by curarine.

PHYSOSTIGMINE OR ESERINE is identical in its action with acetylcholine. As just mentioned, it acts simply by inhibiting the action of the choline esterase, and so permitting the cholinester liberated at the nerve endings to exert its full effect.

ATROPINE annuls parasympathetic effects, and antagonizes the actions of pilocarpine, of muscarine and of the "muscarine" action of acetylcholine. It is believed to act directly upon the effector cell, preventing the action but not the liberation of acetylcholine. It therefore quickens the heart, and paralyzes the sphincter pupillae and ciliary muscles and thus causes pupillary dilatation and failure of accommodation. It suppresses the secretion of saliva, and of the nasal, bronchial and gastric glands. It is inhibitory to the bronchial muscles and lowers the tone of the intestinal musculature. *It also suppresses the secretion of the sweat glands which are innervated by the sympathetic (see p. 948).*

THE CHEMICAL TRANSMISSION OF NERVOUS EFFECTS TO AUTONOMIC EFFECTORS AND SKELETAL MUSCLE

Within the past few years evidence has accumulated which clearly indicates that parasympathetic effects are mediated through a chemical substance liberated at the nerve terminals. This substance is identical in its action with acetylcholine. Experiment has also shown that certain sympathetic endings liberate an adrenaline-like substance (sympathin). Acetylcholine also serves as a chemical transmitter of certain sympathetic effects.

Space does not permit an extended account of the experimental work upon which present day knowledge of these humoral mechanisms is based, but a summary of the more important facts will be attempted. The work of Loewi upon the transmission of cardiac effects (vagal and accelerator) and Cannon's discovery of "sympathin" (p. 691) have already been considered.¹

The experiments to be described involve either (a) a comparison of the effects of autonomic and motor nerve stimulation with the pharmacological actions of acetylcholine or, (b) the stimulation of the autonomic nerves to an organ, e.g., the salivary gland, and testing the venous blood issuing from it, or the fluid with which it has been perfused, for an acetylcholine-like action. In order to prevent the hydrolysis by cholinesterase of acetylcholine after its liberation from the nerve terminals, eserine in a dilution of 1 in 1 million or so is added to the perfusion fluid. The following is a list of the tests employed and the pharmacological effects which indicate the presence of acetylcholine.

(1) *Blood pressure of the cat.* Dilatation of the arterioles and a fall in blood pressure ("muscarine" action). The effect should be annulled by atropine. (2) *Inhibition of the perfused frog's heart or rabbit's auricle* ("muscarine" action annulled by atropine). (3) *Contraction of the voluntary muscle (rectus abdominis) of the frog* ("nicotine" action). (4) *Contraction of the muscle in body wall of the eserinated leech* ("nicotine" action). This test is sensitive to 2 gamma of acetylcholine per liter. (5) The active substance should be inactivated by alkali or by uneserinated blood (which contains cholinesterase).

During nerve stimulation the acetylcholine-

¹ The suggestion that a chemical substance might be liberated from nerve endings was made by Elliott (1904-5), and before him by Du Bois-Reymond, though no direct experimental evidence was offered.

like substance is liberated and enters the blood or perfusion fluid in such minute amounts that its chemical identification is out of the question. Had acetylcholine not been demonstrated by chemical analysis to be a normal constituent of the body, such purely pharmacological tests for its appearance during nerve stimulation would still leave some doubt that it was actually the substance concerned. This doubt was removed by the work of Dale and Dudley who obtained chemically recognizable amounts of this choline ester from the spleen of the horse. It is also present in human placenta and in nervous tissues; only minute amounts are present in blood. That the chemical mediator is actually acetylcholine is now generally accepted. With one exception (namely pyruvylcholine) no choline ester other than acetylcholine has an action quantitatively comparable with that exhibited by the chemical transmitter. Moreover, acetylcholine is the only ester of choline found in animal tissues.

Summary of experimental work relating to the rôle played by acetylcholine in the transmission of nervous effects

(1) *Stimulation of the chorda tympani to salivary glands.* Babkin and his associates found that when the chorda of one side was stimulated a substance entered the blood which caused a fall in blood pressure and secretion from the denervated salivary gland of the opposite side. These effects were abolished by atropine. Similar results have been obtained by others. During stimulation of the chorda of a perfused salivary gland, for example, a substance identical in action with acetylcholine was found by Henderson and Roepke in the perfusion fluid.

(2) *The liberation of acetylcholine from parasympathetic endings in the iris.* When a strong light was thrown into one eye, the other eye being shaded, an acetylcholine-like substance was obtained from the aqueous humor of the illuminated eye but not from the darkened eye (Engelhart).

(3) *Acetylcholine and vasodilator nerves. The hypersensitivity of denervated structures to chemical stimulation.* Many years ago Philipeaux and Vulpian (1863) observed that after section and degeneration of the hypoglossal nerve, stimulation of the chorda tympani going to the tongue caused a peculiar slow and prolonged contraction of the lingual muscles (Vulpian effect) and vasodilatation. Stimulation of the chorda causes no effect upon the normal tongue other than vasodilatation. Acetylcholine also causes this peculiar contraction of the denervated tongue muscles ("nicotine" action) together with vasodilatation ("muscarine" action). It has therefore been suggested that the vasodilatation following chorda stimulation is due to the liberation of acetylcholine from the nerve ter-

minals, and that the Vulpian effect results from the diffusion of the active substance to the muscle fibers rendered sensitive by denervation. A reaction analogous to the Vulpian effect was described by Sherrington, who found that after the muscles of the leg were deprived of their *motor* innervation by sectioning the ventral roots containing fibers for the sciatic nerve, and allowing time for the degeneration of the fibers to occur, stimulation of the sciatic caused the characteristic slow contraction of the muscles. The effect can be duplicated by acetylcholine. Evidence was subsequently obtained which indicated that the nerve fibers concerned ended upon the blood vessels. It was therefore concluded that the effect was due to the liberation of acetylcholine from the sensory fibers which normally carried antidromic vasodilator impulses (p. 235). It now appears, however, from the work of Hinsey and Cutting, that *sympathetic* postganglionic fibers arising from the lumbar and sacral ganglia and reaching the sciatic nerve via the gray rami are responsible. This leads to the suggestion that acetylcholine liberation from *sympathetic* terminals upon the blood vessels causes vasodilatation and the Sherrington phenomenon as a secondary effect due to diffusion of the ester from its site of production to the muscle fibers. The latter as well as the Vulpian effect is intensified by eserine. An effect of the same nature as the Sherrington phenomenon is obtained upon stimulation of the cervical sympathetic after section and degeneration of the facial nerve, viz., dilatation of the vessels of the gums and lips together with contraction of the muscles of the upper lip (Rogowitz).

Another example of increased sensitivity of denervated muscle to acetylcholine is the interesting and suggestive observation made more recently by Bender. After section and degeneration of the 7th nerve in monkeys the denervated facial muscles were found to contract involuntarily when the animal became angry or frightened. This "*fright reaction*" can be duplicated by the injection of acetylcholine and is accentuated by eserine. It is attributed to the release of acetylcholine into the general circulation from some unknown source. The phenomenon recalls the liberation of adrenaline in emotional states and the hypersensitivity to adrenaline or sympathin of the denervated iris. Further examples of the hypersensitivity of denervated structures to acetylcholine, adrenaline and other chemical agents can be cited, e.g., the greater secretory response of the denervated salivary gland to pilocarpine, the hypersensitivity of the pupil to acetylcholine after section of the 3rd nerve and of the nictitating membrane to adrenaline following excision of the superior cervical ganglion. The inhibitory effects of adrenaline (e.g., on the bowel and non-pregnant uterus) are also enhanced by denervation. These and other similar observations have led to the formulation by Cannon of a *law of denervation* which he states in the following terms: "When in a series of efferent neurons a unit is destroyed, increased irritability to chemical

agents develops in the isolated structure or structures, the effect being maximal in the part directly denervated."

If the effects described in the first paragraph of this subsection are actually due to acetylcholine one would expect the vasodilatation ("muscarine" action) to be prevented by atropine. But this is not the case. Though atropine annuls the vasodilator action of acetylcholine it does not prevent the effects of stimulating vasodilator nerves. It has been suggested (Dale), in an effort to explain this discordant fact, that acetylcholine is liberated in such intimate relation to the smooth muscle of the vessel that atropine fails to reach it.

(4) *Acetylcholine as an intermediary of parasympathetic effects to the alimentary tract and bladder.* It has been shown that Ringer's solution in which a beating loop of intestine is immersed is capable of augmenting the activity of another similar loop (Weiland). It has also been found that if the vagus nerve to the intestine is stimulated and a loop then removed and suspended in Ringer's solution, the contractions of this loop are greater than those of a similar one which had not been previously excited in this manner. These experiments suggest that during intestinal activity a substance is liberated by the vagal endings which has an augmenting effect upon the contractions. Evidence for the liberation of acetylcholine by the gastric vagus has recently been obtained by Dale and Feldberg. A substance identical in action with acetylcholine was detected in the venous blood leaving the resting stomach or in the eserinizd fluid perfusing its wall. During vagal stimulation the quantity of the active material was increased four-fold.

An acetylcholine-like substance has also been identified by Henderson and Roepke in the fluid perfusing the bladder during stimulation of its parasympathetic nerves. In the case of the intestine and bladder as in the case of vasodilator nerves, the same discrepancy exists between the action of atropine upon the effects of nerve stimulation and the action of the drug upon the effects of acetylcholine administration. Atropine abolishes the action of acetylcholine when applied artificially to these organs but does not depress the contractions set up by parasympathetic stimulation. Henderson and Roepke conclude from the results of their experiments that, whereas the tone of the intestine and of the bladder is dependent upon the liberation of a choline ester, another mechanism is responsible for the phasic contractions. Atropine, as is well known, depresses the tone of the intestinal and vesical musculatures but exerts no direct effect upon the contractile mechanism.

(5) *The liberation of acetylcholine from sympathetic preganglionic fibers.* Feldberg and Gaddum perfused the superior cervical ganglion with eserinizd fluid. The inflow cannula was inserted into the common carotid artery, all branches of which had been tied except the one to the ganglion. The fluid was collected

from the internal jugular vein, all its tributaries except that from the ganglion having been occluded. During stimulation of the cervical sympathetic trunk below the ganglion the fluid issuing from the vein was found to possess an action identical with that of acetylcholine. When the collected fluid was passed through the ganglion of the opposite side its stimulant action ("nicotine" action) upon this structure was evidenced by a contraction of the nictitating membrane. Fluid collected before or after the period of stimulation showed no such activity.

(6) *Acetylcholine liberation during the discharge of adrenaline.* Stimulation of the sympathetic fiber supplying the adrenal medulla causes an acetylcholine like substance to appear in the blood of the adrenal vein. It has therefore been concluded that acetylcholine acts as a chemical transmitter from the nerve terminals to the medullary cells. It will be recalled that the sympathetic fibers ending in the adrenal are preganglionic, the adrenal cell itself taking the place of the ganglion cell (p. 684). It is mainly the "nicotine" action of acetylcholine (i.e., abolished by a large dose of nicotine but not by atropine) which is exerted upon the adrenal, but there is also a slight "muscarine" action.

(7) *Acetylcholine as the transmitter of effects to the sweat glands.* Though the human sweat glands are innervated by the sympathetic their behavior to drugs is similar to that of structures supplied by the parasympathetic; they are unaffected by adrenaline, stimulated by pilocarpine, and paralyzed by atropine. An experiment of Dale and Feldberg gives an explanation of these discrepancies, or at any rate brings the mechanism of sweat secretion into the general scheme. Excitation of the sympathetic fibers to the foot pads of the cat was followed by sweating and the appearance of acetylcholine in the eserinizd fluid perfusing the paw.

(8) *Chemical transmission of motor nerve impulses to voluntary muscle.* Evidence that acetylcholine is liberated from the terminals of motor nerves and serves as a transmitter of impulses to the muscle fibers has been obtained by Dale and his associates.

(a) Upon rhythmical stimulation of the hypoglossal nerve of the perfused tongue of the cat, acetylcholine appeared consistently in the venous fluid. Similar results were secured with the perfused leg muscles of the dog during stimulation of the ventral spinal roots after excision of the lumbar sympathetic chain.

(b) The sudden injection of a small dose (2 to 10 γ) of acetylcholine into the artery supplying the gastrocnemius of the cat during circulatory arrest caused a sharp contraction of the muscle. This is a "nicotine action" of acetylcholine; it is annulled by curarine but not by atropine. The direct application of a minute amount ($5 \times 10^{-6} \gamma$) of acetylcholine to the motor end-plate of the muscle fiber causes a short sharp tetanic contraction. Ten times this quantity applied

elsewhere to the fiber is ineffective (Buchthal and Lindhard).

(c) The intravenous administration of eserine (0.2 to 0.3 mgm. per kgm.) to a spinal cat caused an increase of 130 per cent in tension of a gastrocnemius twitch provoked by stimulation of the motor nerve. Eserine had no such effect upon the response of denervated muscle to direct stimulation.

The rôle played by potassium ions in synaptic transmission

The injection of small amounts of potassium chloride into the fluid perfusing the superior cervical ganglion stimulates the nerve cells, and the injection of a sub-stimulant dose augments the effect of a series of submaximal stimuli applied to the preganglionic fibers (Feldberg and Vartiainen). When the concentration of potassium chloride is raised to four times the normal, acetylcholine appears in the venous outflow from the ganglion (Feldberg and Brown). It had been reported previously by Beznak that KCl caused the liberation of acetylcholine in the frog's heart. After section of the cervical sympathetic and degeneration of the preganglionic fibers the addition of KCl to the fluid perfusing the superior cervical ganglion, though still causing excitation of the cells, results in the liberation of an insignificant amount of acetylcholine. This fact indicates that the K ion itself (i.e., quite independent of acetylcholine) has a stimulant action upon the ganglion cells. There has been some discussion of the interpretation of these findings in regard to the rôle played by the K ion in the normal conduction in sympathetic ganglia. Brown and Feldberg found, for example, that curarine, which blocks transmission at synaptic junctions, does so by preventing acetylcholine from acting on the ganglion cell; but it actually enhances the response to KCl. The output of acetylcholine from the preganglionic endings was not affected by the poison. These observations suggest that potassium is not directly concerned in the transmission of the effect across the synapse. Brown and Feldberg suggest that the liberation of acetylcholine under normal circumstances is dependent upon the movement of K ions ("a wave of mobilization of K ions") accompanying the preganglionic impulse and that the appearance of K ions at the synapse also conditions the action of acetylcholine upon the ganglion cell.

That calcium also plays an important rôle in the excitation mechanism has been shown by Bronk and his colleagues who found that the absence of calcium ions caused a long continued spontaneous discharge from sympathetic ganglion cells. Bronk has also reported that doubling the calcium concentration greatly reduces the frequency of the impulses discharged by nerve cells stimulated by acetylcholine. Lowering the concentration of potassium had a similar effect. Either lowering the concentration of calcium or increasing that of potassium increased the frequency of the impulses. Harvey and McIntosh found that

absence of calcium from the fluid perfusing a ganglion results in failure of synaptic transmission and of acetylcholine liberation from the preganglionic terminals. The absence of calcium was not followed by spontaneous activity of the ganglion cells unless potassium was present. It did not result, therefore, when the ganglion was perfused with a 0.9 per cent sodium chloride solution. These observers conclude from their experiments that calcium is necessary in order that potassium can act to liberate acetylcholine from the nerve endings. Impairment of transmission at the myoneural junction has been observed by Brown and Harvey in young animals kept on a diet deficient in calcium.

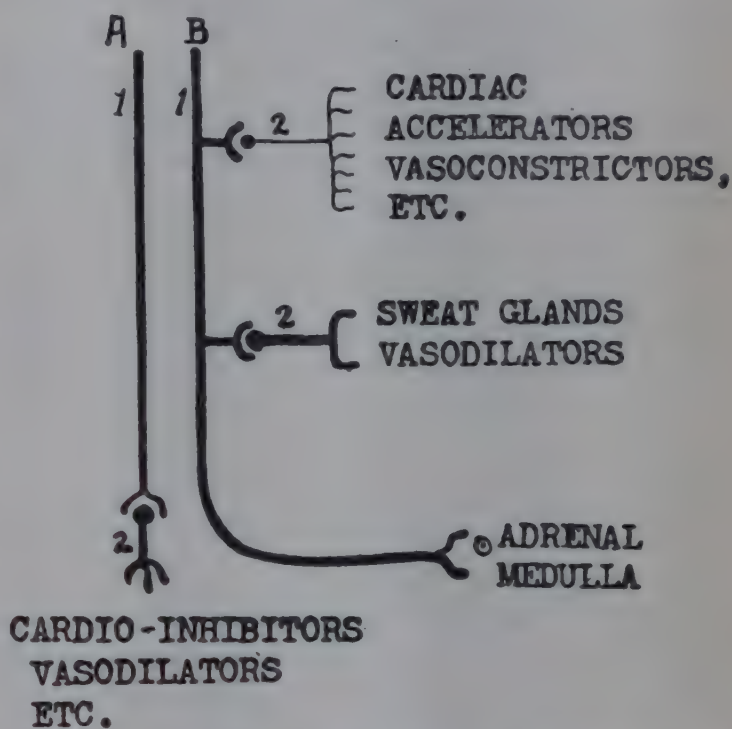


FIG. 391. Diagram showing the distribution of cholinergic and adrenergic fibers. A, parasympathetic; B, sympathetic; 1, preganglionic; 2, postganglionic, heavy lines, cholinergic; light lines, adrenergic.

From the results of the investigations cited in the foregoing paragraphs a summary can now be given in respect to the liberation of humoral agents from autonomic nerve endings (fig. 391). Acetylcholine is liberated at the endings of parasympathetic fibers such as those of the chorda tympani going to the salivary glands, and of those innervating the sphincter pupillae, heart, stomach, intestine, bronchioles, bladder, erectile tissue, etc. It is also probably set free at the terminations of both parasympathetic and sympathetic vasodilator nerves and of parasympathetic nerves to the intestine and bladder. It is apparently the transmitter of effects between the sympathetic *preganglionic* fiber and the ganglion cell. The nerve impulse reaching the preganglionic terminal liberates acetylcholine which then stimulates the ganglion cell ("nicotine" action). The effect of

acetylcholine upon the ganglion cell appears to be potentiated by potassium ions. The impulse set up in the nerve cell passes along the *postganglionic* fiber and causes the liberation of an adrenaline-like substance from its terminal. Since it is known that each nerve impulse transmitted along a preganglionic fiber causes only one impulse to be discharged along the postganglionic fiber, it is assumed that a fresh quantity of acetylcholine is liberated by each preganglionic impulse and then destroyed by the action of the cholinesterase. It is probable, though so far unproved, that acetylcholine serves as a chemical transmitter between parasympathetic preganglionic fibers and the parasympathetic ganglion cell.

Since anatomical terms fail to express these physiological conceptions Dale suggests that the fibers which liberate acetylcholine be called *cholinergic*, and the term *adrenergic* be used for those which liberate an adrenaline-like substance (sympathin). Thus (a) parasympathetic postganglionic fibers, (b) postganglionic sympathetic fibers supplying the sweat glands and uterus, and (c) sympathetic preganglionic fibers are cholinergic—the “muscarine” action being prominent in the first two instances, the “nicotine” action in the last. (d) The parasympathetic preganglionic fibers and the postganglionic sympathetic fibers causing vasodilatation (see p. 234) are also cholinergic. Postganglionic sympathetic fibers, e.g., to the heart, intestine, etc., as well as those causing vasoconstriction, are adrenergic.

The relation of acetylcholine to synaptic and neuromuscular transmission

The chemical theory in all its aspects has not received universal acceptance. The evidence is virtually conclusive that in the slower types of transmission (muscarine-like action, e.g., at vagal and other postganglionic terminals) acetylcholine plays an essential rôle in the nervous effects. With regard to the more rapid types of transmission (nicotine-like action, e.g., at synapses between preganglionic fibers and ganglion cells, synapses in the central nervous system and their equivalent in striated muscle (namely, the myoneural junction) opinion has been sharply divided. Dale and his colleagues have maintained that in these instances, also, acetylcholine served as the transmitting agent. Eccles criticized this view, mainly on the ground that whereas the action of the cardiac vagus is prolonged, the acetylcholine persisting for seconds, in the synapse a chemical transmitter if it exists must be removed from its site of action within a few milliseconds, i.e., within the refractory period of the postganglionic neuron. He and others have doubted that sufficient quantities of cholinesterase were

produced in the required time. Scepticism was also expressed that acetylcholine, in quantities great enough to stimulate the ganglion cell, could be formed so rapidly. These objections have been met to a large extent by the work of Marnay and Nachmansohn who have furnished evidence of a high concentration of cholinesterase at the motor end-plates. According to their estimation, the concentration of enzyme at these sites is many thousand times greater than in the rest of the muscle.

The rate of production of the enzyme at the muscle end-plates is the basis for the estimation of the formation of its substrate, acetylcholine. In other words, the rate at which acetylcholine is removed is taken as a measure of its production. In this way it has been estimated that about 2×10^{-6} micrograms of acetylcholine can be split at a single nerve ending of the frog's sartorius muscle during the refractory period. This amount which corresponds to the production of 8×10^9 molecules of acetylcholine, is considered to be more than sufficient to stimulate. It has also been found that in a sympathetic ganglion from 3 to 6×10^{10} molecules of the ester can be hydrolyzed within a millisecond.

Those who supported the classical theory of neuromuscular and synaptic transmission, namely, that the action currents set up in the motor nerve or preganglionic fiber excite the muscle or the ganglion cell, point out that the interval between the arrival of the nerve impulse at the motor end-plate and the beginning of the propagated disturbance in the muscle (end-plate delay) is of about the same duration as the “spike” potential. Erlanger has shown also that the nerve impulse can excite the section of nerve beyond a blocked region of from 1 to 2 millimeters in length. He argued, therefore, that it was unreasonable to maintain that discontinuity at a synapse (or presumably at the myoneural junction) would prevent transmission of the impulse. Such facts advanced by the proponents of the electrical theory could not be disregarded, yet, it was difficult to believe that the liberation of acetylcholine by nerve impulses, a fact proved beyond dispute, and the relatively high concentration of cholinesterase at the precise site where it could play an essential rôle in the chemical mechanism are merely incidental and without any physiological significance.

Researches within the last few years have brought these two views into harmony. It has been shown that acetylcholine is formed not only at the terminals of the nerve but also along its course during the passage of the impulse. The ester is concentrated in the outer layers of the fiber, not in the axis cylinder.

Acetylcholine is no longer looked upon simply as a transmitter of effects from the nerve terminal across the synapse. The electrical change and the production of acetylcholine are now considered as two inseparable parts of one process. This applies to transmission at synapses, ganglionic or central, neuromuscular junctions, autonomic terminals and to the conduction of

the impulse in the nerve fiber. The liberation of acetylcholine at central synapses has been demonstrated by Chang. Several observations showing the importance of acetylcholine in neural and neuromuscular processes could be cited. For example, a high concentration of the ester has been found to take place at an early stage of embryonic development, at a time when the muscle end-plates make their appearance, when the first muscular movements occur and when the nervous centers become active. Also, in the brain and cord, the gray matter, which is composed mainly of cell bodies and synapses, as well as the retina and the basal ganglia, the concentration of cholinesterase is many times greater than in the white matter. The synthesis of acetylcholine by brain slices incubated *in vitro* has been demonstrated by Quastel and his colleagues.

The close relationship between acetylcholine metabolism and the E.M.F. of the action potential has been shown clearly by Nachmansohn and his associates in a study of the electric organs of such fish as the electric eel and torpedo. These organs can discharge an electric shock which in some of the larger species amounts to from 400 to 800 volts. The electric organ is composed of plate-like structures arranged in series or columns which are believed to have evolved from the end-plates of skeletal muscle. They resemble in their arrangement a voltaic pile. One side only of each plate is innervated, and this side becomes negative during activity. The other side is positive. High concentrations of cholinesterase are produced in these organs. In some instances several kilograms are formed in an hour, or an amount three or more times the weight of the organ itself. A close correlation has been shown by Nachmansohn and his colleagues to exist in the electric organ of *Electrophorus electricus*, between the number of plates per cm., the E.M.F. per cm. and the concentration of cholinesterase. There remains little doubt that the production of acetylcholine is closely associated with the activation and electrical discharge of these organs. The relationship does not imply that acetylcholine generates E.M.F. directly by an action on the surface at a synapse or myoneural junction. Since $V = E - IR$, the ester might act by reducing the resistance at the surface.

That the action potential is associated with a change in resistance has been shown by Cole and Curtis. Conduction is conceived as occurring in the following manner. Acetylcholine by altering the resistance causes the resting potential to be abolished or reversed. Thus, an electric current is set up which activates the adjacent section of the nerve where the same process is repeated and an impulse is propagated along the fiber (see p. 791).

AFFECTIONS OF AUTONOMIC NERVES

HORNER'S SYNDROME is the name given to the group of effects resulting from section or paralysis of the cervical sympathetic. They are: (a) *Ptosis* (drooping of eyelid) and *enophthalmos* (recession of the eyeball) due to paralysis of the smooth muscle of the upper lid and orbit respectively; reduction in intraocular pressure. (b) *Constriction of the pupil* (myosis). The pupil of the affected side is smaller than its fellow of the opposite side as a result of the unopposed tonic action of the pupillo-constrictor center (see p. 1012). (c) *Vasodilatation, higher temperature and absence of sweating* over the affected side of the face. Irritation of the cervical sympathetic tends to cause the opposite effects, namely, widened palpebral fissure, exophthalmos, dilated pupil (mydriasis) and excessive secretion of sweat on the affected side. In the dog stimulation of the cervical sympathetic causes marked protrusion of the eyeball. The movement is due to the contraction of the circularly disposed smooth muscle fibers in the fascia bulbi. A lesion of the brain-stem or spinal cord may interrupt the central course of the sympathetic fibers to the head, with the production of Horner's syndrome.

The relation of the autonomic system to Raynaud's disease (p. 254), asthma (p. 366), megacolon (p. 508) and spastic states of the skeletal muscles (p. 825) has been considered in other sections.

SECTION IX. THE SPECIAL SENSES

CHAPTER LXXIV

THE PHYSIOLOGY OF VISION. STRUCTURE OF THE EYE. DUPLICITY THEORY. REACTIONS OF THE RETINA; SUBJECTIVE PHENOMENA

ANATOMICAL OUTLINE OF THE EYE

The human eyeball (bulb or globe of the eye) is approximately spherical, being slightly flattened from above down. In the adult it measures to about 24 mm. in its anteroposterior and transverse diameters and 23.5 mm. in its vertical diameter. It is compounded of the segments of two spheres, its posterior $\frac{1}{2}$ being the large segment of a sphere with a radius of about 8 mm. The center of the anterior curvature of the eyeball is called its *anterior pole* and the corresponding point on the posterior surface the *posterior pole*. A straight line joining the two poles is known as the *optic axis*. The visual axis passes through the cornea a little to the nasal side of its center of curvature and the fovea centralis; the optic and visual axes therefore cross at a point a little behind the center of the lens.¹ The circumference of the eyeball midway between the two poles is termed the *equator*. Any imaginary circle drawn to pass through both poles of the eye is called a *meridian*. The *optic nerve* (p. 1008) enters the eyeball a little to the inner side of the posterior pole. The optic axes are nearly parallel, converging only slightly behind, whereas the axes of the optic nerves followed backwards converge sharply towards the center of the *dorsum sellae* of the sphenoid bone (see fig. 392).

A thin fibrous membrane—the *fascia bulbi* or *capsule of Tenon*—encloses the globe from the entrance of the optic nerve to just behind the circumference of the cornea where it blends with the outer coat (sclerotic) of the eyeball. The *fascia bulbi* is pierced a little in front of the equator of the globe by the ocular muscles; it blends with the sheaths of these muscles. Fascial slips (*check ligaments*) pass from the muscle sheaths, especially those of the external and internal recti, to the walls of the orbit and serve, it is believed, to check the movements of the muscles. In the region surrounding the optic nerve entrance the *fascia bulbi* is pierced by the ciliary vessels and nerves and just behind the equator by the vortex veins. The space between the *fascia bulbi* and the globe is occupied by a meshwork of fine areolar tissue, the eyeball thus lies in a cushioned socket, separated from the other contents of the orbit.

THE CONJUNCTIVAL AND LACRYMAL APPARATUS. The exposed part of the eyeball is covered by delicate mucous membrane—the *conjunctiva*—which is reflected

on to the inner surfaces of the eyelids. The ocular surfaces are lubricated and kept clean of fluid secreted by the *lacrymal gland* (fig. 3). The *lacrymal gland* is about the size and shape of an almond. It lies under the shelter of the bone of the upper and outer part of the orbit (i.e., the *lacrimal process* of the frontal bone). It is of the *serous* type, somewhat resembling in structure a *salivary gland*; its secretion—the tears—is carried through a number of fine ducts into the *conjunctival fornix*. The secretion is a clear watery fluid having, according to Ridley, the following composition.

Water	98
Total solids	1
Ash	1
Total N	0
Non-protein N	0
Urea	0
Protein (albumin and globulin)	0
Sugar	0
Chlorides (as NaCl)	0
Sodium as Na ₂ O	0
Potassium as K ₂ O	0
Ammonia	0

A sample of tears collected from the *conjunctival* surface also contains traces of mucus secreted by the *conjunctiva* itself.

Several small accessory *lacrymal glands* are present in the *conjunctival fornices*; their secretion serves for lubrication and cleansing under ordinary circumstances. The main glands are called into play only upon special occasions, e.g., crying, or in response to irritation of the *conjunctiva*.

The winking movements of the lids spread the tears over the *conjunctival surfaces*; the fluid is directed into the *lacrymal lake*—a small triangular area lying in the angle bounded by the innermost portions of the eyelids. The center of the *lacrymal lake* is occupied by a pink structure, composed of modified skin, containing sebaceous glands and a few slender hairs. The tears are drained from the *lacrymal lake* by two small ducts—the *lacrymal ducts*. The minute orifices of these ducts—the *puncta lacrymalis*—may be seen one on the inner margin of each lid. The *lacrymal ducts* lead into the *nasolacrymal duct*; this opens into the

¹ The angle formed by the intersection of the optic axis with the visual axis is about 5° and is referred to as the *angle alpha*.

of the nose; its upper blind end is termed the *lacrimal sac*.

Secretory fibers to the lacrimal gland are derived from the parasympathetic. They arise from the superior salivary nucleus, or, according to some, from a group of cells (*lacrimal nucleus*) in close relation to the former. The fibers leave the brain in the

nerve—a branch of the ophthalmic. The lacrimal nerve thus receives the parasympathetic fibers and delivers them to the lacrimal gland; it also carries sensory fibers to the gland.

Lacrymation is induced reflexly by stimulation of the nerve endings of the cornea or conjunctiva (ophthalmic division of the 5th nerve). The reflex is annulled by anesthetization of the surface of the eye, by section of the sensory nerves or of the great superficial petrosal nerve, or by blockage of the sphenopalatine ganglion. Emotional lacrymation is not affected by local anesthetization nor by section of the ophthalmic division of the 5th nerve, but is abolished by section of the great superficial petrosal nerve or by blockage of the sphenopalatine ganglion. The sympathetic does not furnish secretory fibers to the lacrimal gland. Excessive lacrymation may follow a lesion of the facial fibers central to the facial ganglion. Defective or complete absence of a lacrymatory response, either psychic or reflex is seen, though very rarely, as a congenital anomaly.

THE TUNICS OF THE EYEBALL

The wall of the eye is composed of three concentric layers or tunics. (1) An outer or fibrous tunic—the *sclera and cornea*, (2) a middle vascular tunic—the *choroid, ciliary body and iris*, and (3) a nervous tunic—the *retina* (see fig. 392).

THE OUTER OR FIBROUS TUNIC. [The posterior $\frac{1}{2}$ of this coat is hard, tough and opaque and is called the *sclera*; it is composed of white fibrous tissue and fine elastic fibers. Its anterior $\frac{1}{2}$ is perfectly transparent and is called the *cornea*. The sclera appears in front as the so-called "white of the eye." The point where it joins the cornea—the *sclerocorneal junction*—is marked by a faint groove (see p. 1003). Where it is pierced by the optic nerve is reduced to a thin membrane containing perforations for the transmission of the retinal vessels and the bundles of nerve fibers. This part of the outer tunic, known as the *lamina cribrosa*, is the weakest part of the wall of the globe and is the first to yield to a persistently high intra-ocular pressure (see Glaucoma, p. 1004), producing the so-called "cupping" of the optic disc. The cornea is convex anteriorly, being the small segment of a sphere having a radius of about 7.7 mm.² It is almost circular in circumference, measuring 11 mm. and 12 mm. respectively in its vertical and horizontal meridians. It is from 0.5 mm. to 1 mm. in thickness. The cornea is composed of five layers in the following order from before backwards; (a) the corneal epithelium, (b) the anterior elastic lamina of Bowman, (c) the substantia propria, (d) the posterior elastic lamina of Descemet, and (e) a layer of endothelial cells (fig. 394).

The corneal epithelium is continuous with that of the

² The peripheral zone is somewhat flattened as compared with the central portion; the former has a radius of about 6.8 mm.

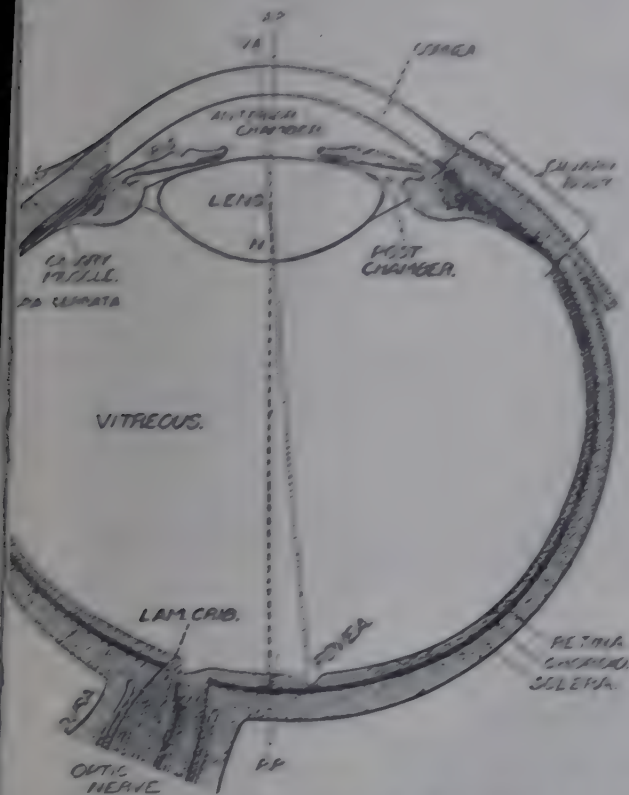


FIG. 392. Horizontal section of the eye. P. P., posterior pole; A. P., anterior pole; V. A., visual axis (Wolff, modified from Salzmann.)



FIG. 393. The lacrimal apparatus. 1, lacrimal gland; 2, lacrimal sac; 3, nasolacrimal duct. Region cut off by interrupted line indicates the position of the lacrimal gland.

intermedius of Wrisberg, the sensory root of the 5th nerve. They pass to the geniculate ganglion which they join in the great petrosal nerve (see fig. 365, p. 861). The sensory root of the 5th nerve joins the deep petrosal nerve to form the sphenopalatine ganglion. The fibers of the sphenopalatine ganglion join the pterygoid canal (Vidian nerve). The fibers are conveyed in the latter nerve to the sphenopalatine ganglion and thence into the zygomatic branch of the 5th nerve. A branch of the zygomatic nerve (zygomaticotemporal) anastomoses with the lacrimal

conjunctiva; it consists of several strata of cells of different sizes and shapes. Columnar cells compose the deepest layer; this is overlaid by two or three layers of polyhedral cells. The cells of the superficial three or four layers are of the squamous type. The *substantia propria* is a tough transparent membrane consisting of a number of flattened lamellae composed of bundles of modified connective tissue fibers continuous with those of the sclera. The *anterior elastic lamina of Bowman* and the *posterior elastic lamina of Descemet* bound

through the anterior elastic lamina where they form a subepithelial plexus; nerve filaments can be traced from the latter to the epithelial cells. The pain fibers have a very low threshold being aroused by very minor forms of stimulation. This has led to the general belief that the cornea is devoid of touch receptors and that stimuli which give a sensation of touch when applied to the skin are painful if applied to the cornea. It is claimed, however, that certain weak and innocuous

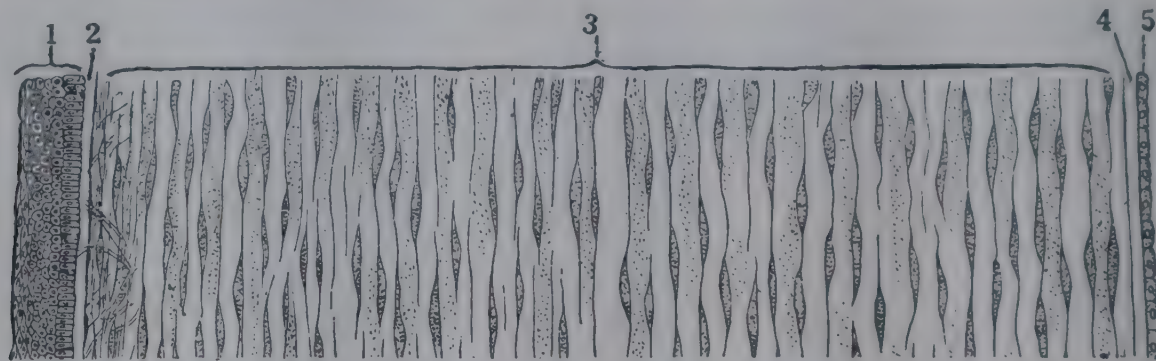


FIG. 394. Section of human cornea; 1, epithelium; 2, anterior elastic lamina; 3, substantia propria; 4, posterior elastic lamina; 5, endothelium of the anterior chamber. (After Waldeyer, modified.)

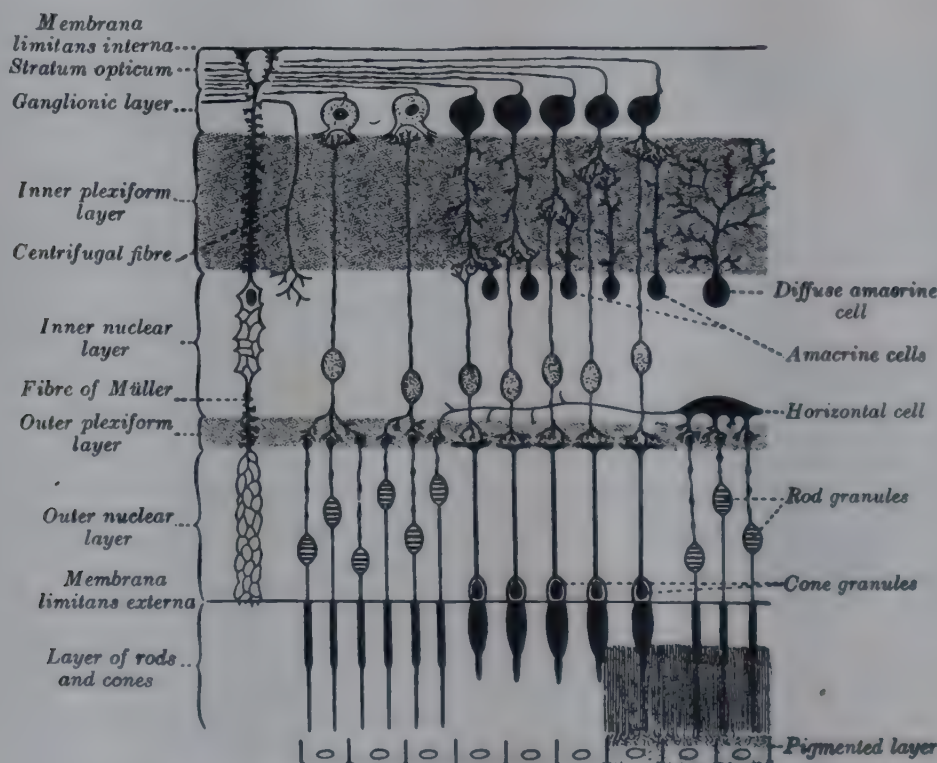


FIG. 395. Layers of retina. (After Cajal.)

the corresponding aspects of the substantia propria. At the circumference of the cornea the posterior elastic lamina breaks up into fibers which are continued into the pectinate ligament (p. 1003). The cornea is devoid of blood vessels; it receives nourishment from lymph derived from vessels at its margin, and which percolates through the spaces between its cells. It is supplied around its circumference by a rich plexus of pain fibers. Fine non-medullated filaments derived from this plexus pass through the posterior elastic lamina and form a second plexus in the substantia propria (stroma plexus). From the stroma plexus fibers proceed outwards

stimulating agents, such as a jet of fluid impinging upon the cornea, arouse a sensation of touch alone.

The MIDDLE OR VASCULAR LAYER consists from behind forwards of the *choroid*, *ciliary body* and the *iris*. The choroid is composed of a rich capillary plexus and the numerous small arteries and veins leading to and from it. It is dark brown in color, due to the presence of pigment cells, and forms the middle layer of the posterior $\frac{2}{3}$ of the globe; it terminates anteriorly at the level of the ora serrata of the retina. The ciliary body is described on p. 993 and the iris on p. 1012.

THE NERVOUS TUNIC OR RETINA. The retina is

composed of seven layers of *nervous elements*, an outermost layer of *pigment cells* and two *supporting membranes*. The following is a list of the ten retinal layers from within outwards (see also fig. 395).

1. *Internal limiting membrane*
2. Layer of optic nerve fibers (stratum opticum)
3. Layer of ganglion cells
4. Inner plexiform or reticular layer
5. Inner nuclear layer
6. Outer plexiform or reticular layer
7. Outer nuclear layer
8. *External limiting membrane*
9. Layer of rods and cones
10. Pigment layer (stratum pigmenti)

The *layer of optic nerve fibers* is composed mainly of the naked axons of the ganglion cells composing the subjacent layer. They make a sharp turn a short distance from their origins and converging towards the posterior part of the globe form the optic nerve.

The *layer of ganglion cells*. There are several (five at least) varieties of these cells. Some are large (giant ganglion cells), others quite small (midget ganglion cells). They also differ in shape; oval, pyriform and multipolar forms can be distinguished. The axons of the ganglion cells compose the first layer mentioned above; their dendrites pass outwards to ramify in the outer plexiform layer where they form synaptic connections with the bipolar cells (see below). Each ganglion cell is synaptically connected to a number of bipolar cells, and through such relations with a large number of visual receptors. One type of ganglion cell of small size, namely, the midget ganglion cell, though it is connected with several diffuse bipolar cells, forms connections with only one midget bipolar.

The *inner plexiform layer* is made up mainly of the dendrites belonging to the ganglion cells and to the cells of the inner nuclear layer. There are, in addition, a few small horizontal nerve cells possessing short branching processes.

The *inner nuclear layer* is constituted of three types of cell. (a) *Bipolar cells*. These possess oval bodies and two long slender processes which arise from opposite poles. There are two main varieties. (i) The *diffuse bipolars* are the most numerous. Their outwardly directed processes (dendrites) synapse with both rods and cones. The other process connects with a ganglion cell. Their dendritic processes show considerable overlapping. (ii) "Midget" bipolars are much smaller and less numerous. Their dendrites do not overlap. In the foveal region each cell synapses with a cone cell but in the extrafoveal retina several cones are synaptically connected with a single midget bipolar. (b) *Horizontal cells*. These are small flattened stellate or larger irregularly shaped elements whose axons run horizontally. They are purely associative in function, their short dendritic processes forming contact with a cone fiber, and their axons to a more distant group of rods and cones. (c) "*Amacrine*" cells. Many of these appear to possess no axons. Their dendritic processes

for the most part ramify in the inner plexiform layer (*diffuse* type). The dendrites of others do not leave the inner nuclear layer (*stratified* type). The axons of some can be seen ramifying in the outer plexiform layer. The polarity of the amacrine cells appears to be in the centrifugal direction, and, therefore, opposite to that of the bipolar and ganglion cells, which convey impulses centripetally.

The *outer plexiform layer* is made up of the ramifications of the process of the bipolar and horizontal cells of the inner nuclear layer and the terminations of the rod fibers and cone fibers.

The *outer nuclear layer* is composed of the cone granules and fibers and the rod granules and fibers.

The nervous elements of the various layers are supported by a framework of fibers of neuroglial character (sustentacular fibers of Mueller). They extend from the inner aspect of the stratum opticum where they constitute the *internal limiting membrane* to the bases of the rods and cones where they break up into a fine feltwork of fibers to form the *external limiting membrane*.

The *layer of rods and cones*. The *rod and cone cells* (fig. 396) are the visual receptors. Both these elements lie with their long axes perpendicular to the retinal surface. The rod cell (40μ to 60μ long) consists of two well-defined portions, a cylindrical outer segment—the *rod*—which extends from the external limiting membrane to the pigment layer, and an inner segment—the *rod fiber*. The latter is a long slender filament swollen at a variable distance along its course by the cell nucleus—the so-called *rod granule*. The inner end of the rod fiber shows a slight enlargement called the *end button* or *spherule* which makes connection with the arborizations of the bipolar and horizontal cells in the outer plexiform layer. The rod itself shows two segments of about equal length, but the outer one is only about half the thickness of the inner and is marked by transverse striae. The two parts of the rod differ chemically, each reacting in its own way to certain dyes; the outer thinner portion is composed of a myelin-like material, the inner, of protoplasm. The outer segment breaks up after death along the striae just mentioned into tiny transverse plates; this part of the rod alone contains a reddish pigment—the *visual purple* or *rhodopsin* (p. 970).

The cone cell consists of a pyramidal portion—the *cone*—situated on the outer side of the external limiting membrane with its pointed end directed towards the pigment layer, and an inner segment—the *cone fiber*—which varies in length and thickness according to the part of the retina in which it is situated. The cone fibers contain the nuclei; these are the *cone granules* already mentioned with the rod granules as being the chief elements of the outer nuclear layer. The cone cells vary from 28 to 85 microns in length in different parts of the retina, and from 2.5 to 7.5 microns in thickness.

The number of receptors in the human retina according to most recent estimates is about 115,000,000 rods

and 6,500,000 cones. In the fovea each cone is believed to have its own nerve fiber, whereas in the peripheral retina a single fiber is distributed to about 80 receptors. It is evident that light in order to reach the rod and cone layer must pass through all the other nervous layers. The retina has been compared to a transparent carpet laid upside down (Walls). The pile then corresponds to the visual receptors and the jute backing to the maze of nerve fibers which support the visual and integrate the impulses initiated in them.

The *pigment layer* consists of a single row of epithelial cells containing mobile rod-shaped granules of a dark brown melanin-like pigment called *fuchsin*. The outer surfaces of the pigment cells are hexagonal in outline (fig. 396) and are firmly attached to the choroid. From

expands, while the proximal portion remains narrow and is termed the *optic stalk*. As development proceeds the outer wall of the optic vesicle collapses and becomes invaginated; finally, it seems the inner wall and with it, thus a two-layered cup-shaped structure—the *optic cup*—is formed. The deep layer consists of a single row of epithelial cells which acquire pigment, is seen in the adult retina as the *stratum pigmentum*. The invaginated wall becomes thickened, and from it are developed the nervous layers of the retina. At birth the nervous layers (retina proper) can be readily stripped up from the pigment cells which remain attached to the choroid. The membrane freshly detached from the pigment layer appears reddish (due to presence of visual purple) and, transparent when shielded from strong light. Upon exposure to bright light, however, it rapidly becomes colorless (bleached) and clouded. The line of union between the two walls of the optic cup is always a weak part in the adult retina and in the living eye detachment of the retina from the pigment layer is not an uncommon accident.

The retina proper extends from the margins of the optic papilla (see below) to just behind the ciliary body. At this point it ends abruptly in a dentated border—the *ora serrata* (see fig. 447, p. 993). Its thickness diminishes progressively from the optic papilla (where it measures about 0.4 mm.) to the dentate border where it is only 0.09 mm. thick. The pigment layer is continued forwards from the *ora serrata* over the deep surface of ciliary body (*pars ciliaris retinae*) and iris (*pars iridica retinae*). Two retinal areas require special mention—the *optic disc* and the *macula lutea* with the *fovea centralis*.

The *optic disc* is situated about 3 mm. to the nasal side of and a little above the posterior pole of the eyeball; it has a diameter of about 1.5 mm. in man. When viewed in the human eye subject by means of the ophthalmoscope (p. 988) it appears as a pink circular area fading to a creamy white toward the center. It is pierced near its center by the retinal vessels—the *arteria centralis retinae* and its accompanying vein (Pl. 2, opposite p. 989). The circumference of the optic disc is elevated to form the *optic papilla*. The central depressed part is known as the *physiological cup* or the *excavation of the optic nerve*. The vessels climb up the inside of the cup to reach the retina. All layers of the retina except the nerve fiber layer are absent from the optic disc. It is therefore totally insensitive to light and is known as the *blind spot* of the retina. The reader is referred to fig. 463 for a demonstration of the blind spot in his own eye.

The macula lutea. A small diffuse yellow area called the *macula lutea* (yellow spot) is seen in the retina a little to the temporal side of the posterior pole of the globe, i.e., about 3.5 mm. from the outer edge of the optic disc. Its color is due to the presence of a yellow pigment which, like the visual purple, is bleached by light though much less readily. The central zone of the macula lutea is depressed and is referred to as the *fovea*

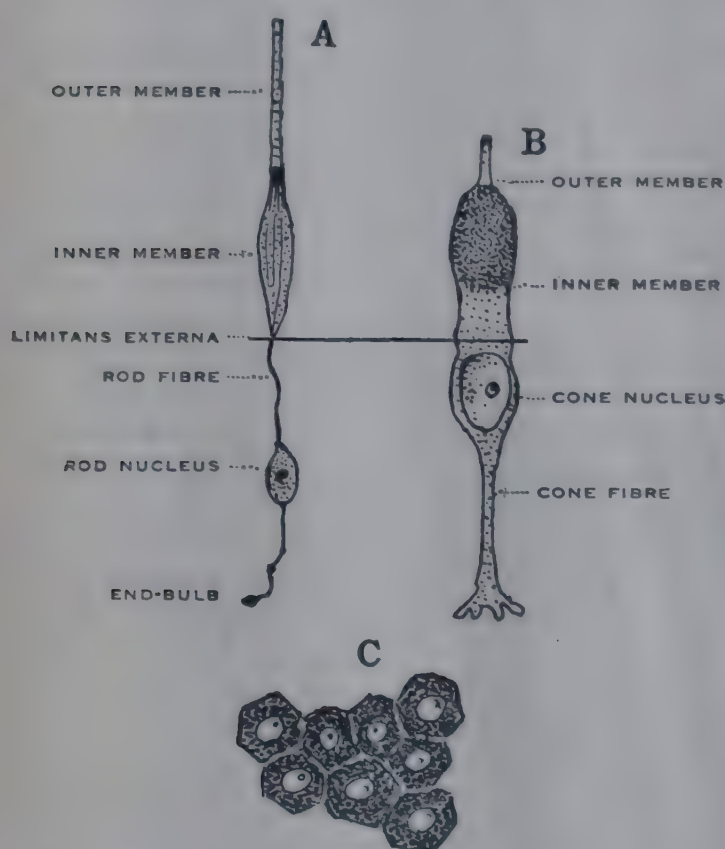


FIG. 396. A, rod; B, cone; C, pigment cells viewed from the surface.

their inner portions fine processes arise which are insinuated between the rods and cones. In darkness or dim light the pigment granules are aggregated in the inner half or so of the cell body but in certain species, e.g., the frog and fishes—not in mammals—(p. 973), illumination of the eye causes them to move into the processes between the visual cells. The pigment serves, like the black paint on the inside of a camera, to absorb light which otherwise would be diffused and cause blurring of the retinal image. In albinos the hexagonal cells are free from pigment.

DEVELOPMENT OF THE RETINA AND DESCRIPTION OF ITS GROSS APPEARANCE. Knowledge of the origin of the retina is an important step towards an understanding of its functions. It is developed from a hollow outgrowth of the rudimentary fore-brain called the *optic vesicle*. The distal portion of this diverticulum

macula lutea. This is the region of the retina concerned with acute vision; in man it has a diameter of about 0.44 mm. (Wolfrum). The depression is due to the extreme thinning of the retina proper at this point, brought about by the disappearance of the nerve fiber, ganglion cell, inner plexiform, inner nuclear and outer plexiform layers. The elements which compose these layers are absent peripherally, leaving only the cone cells which are here exceptionally long (85μ) and slender (fig. 397). At the bottom of the fovea the thickness of the retina is only 0.1 mm. Moreover, the cone fibers of this region are elongated and, instead of passing perpendicularly inwards, incline obliquely to connect with the bipolar cells around the margins of the fovea. In this region a layer is formed which, though it corresponds to the outer nuclear layer, differs in appearance from that of any other part of the retina. It is called the *outer fiber layer of Henle*. In this region it alone overlies the pigment layer. The pigment layer is exceptionally well-developed at the fovea.

THE OCULAR CIRCULATION. Thirty-three separate arteries enter the globe. The *retina* is supplied by the *arteria centralis retinae*, a branch of the ophthalmic artery. The central artery with its companion vein pierces the optic nerve about 1.25 cm. behind the eyeball and bending sharply runs forwards in the center of the nerve. Perforating the lamina cribrosa it appears inside the eyeball at the center of the optic disc. It immediately divides into two main branches which redivide to form a vascular network, the finer channels ending in a capillary plexus which extends outwards as far as the inner nuclear layer. The fovea itself is devoid of vessels. The vessels of the *choroid* are derived from the long and short posterior ciliary arteries, branches of the ophthalmic, and from the anterior ciliary arteries which are twigs of the lacrymal branch of the ophthalmic. The two long posterior ciliary arteries pierce the sclera a short distance from the optic nerve and, running forwards on either side of the globe between the choroid and the sclera, anastomose with

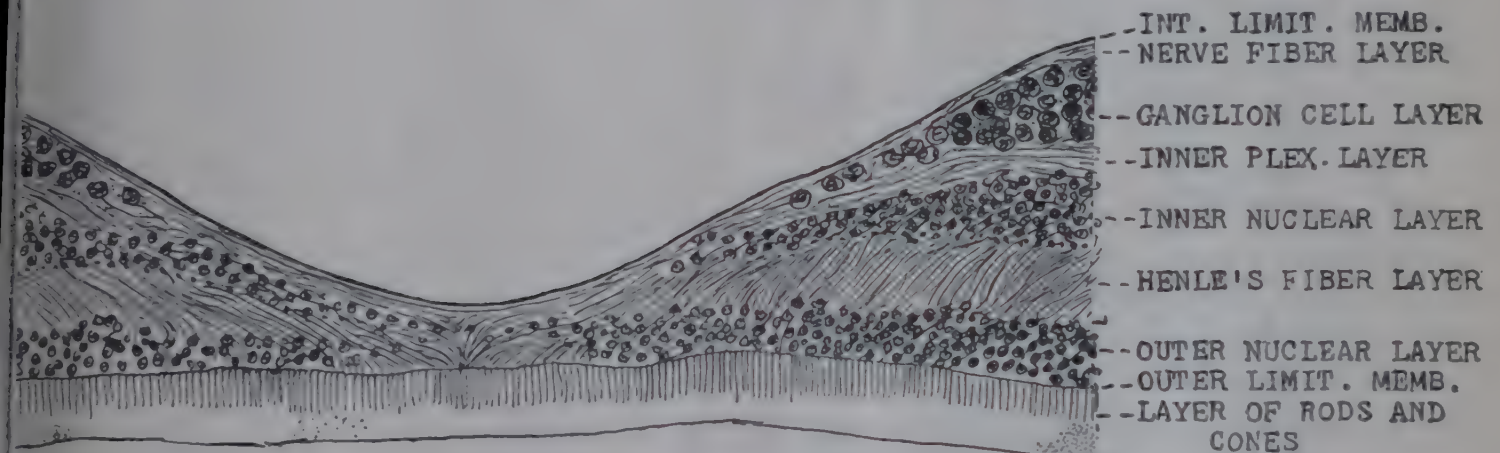


FIG. 397. Section through the centre of the fovea centralis. (From Wolff, after Eisler.)

As a result of the displacement of the retinal elements from the fovea, and of the greater size of the ganglion cells, the macular retina is unusually thick around the foveal margins.

The fovea is rod-free. In the remainder of the retina the cones diminish progressively in number from the foveal margin to the periphery, while the rods increase proportionately. The macula immediately surrounding the fovea is nearly but not quite rod-free. In some animals, e.g., the rat and certain night-flying birds, the retina throughout contains only rods; in others, especially day birds, rods are almost entirely absent.

It must never be forgotten that the retina is an outgrowth of the brain and retains the structural and functional characteristics of nervous tissue. The neurons composing its several layers are connected through synaptic junctions, and such phenomena as temporal and spatial summation, latency, inhibition, convergence and occlusion (see Chapter LXV) have been demonstrated in the retina. As already mentioned, a single ganglion cell of the retina can receive over convergent pathways impulses from a number of visual receptors.

branches of the short posterior ciliary arteries and of the anterior ciliary artery to form a vascular ring (*circulus arteriosus major*) which encircles the periphery of the iris. Branches pass from this vascular circle along converging lines through the tissue of the iris to the pupillary margin; here they join to form a smaller arterial ring (*circulus arteriosus minor*). The short posterior ciliary arteries perforate the sclera around the optic nerve and supply the choroid and ciliary processes. The anterior ciliary arteries and their companion veins pierce the globe a little behind the sclerocorneal junction. The blood is returned from the choroid by a system of veins in the outer choroidal layer. From their whorl-like arrangement they are termed the *vortex veins* (*venae vorticales*). The smaller and medium sized vessels of this system become confluent to form four trunks which penetrate the sclera and appear on the surface of the globe equidistant from one another just behind its equator. These vessels and the anterior ciliary veins drain into the ophthalmic veins. The central vein of the retina empties into the cavernous sinus either directly or through one of the ophthalmic veins (p. 990).

In man the pressure in the central artery of the retina is from 70 to 85 mm. Hg systolic and from 40 to 50 mm. diastolic. But owing to the presence of the intra-ocular fluid and the resistant nature of the sclerotic coat, pulsation of the retinal artery as observed by ophthalmoscopic examination is slight. The pressure in the retinal artery of the intact globe may be determined by the method of Bailliart which consists in observing the vessel with the ophthalmoscope while a measured pressure is made upon the globe. Maximal pulsation is taken as indicating the diastolic level and the disappearance of pulsation as an index of the systolic pressure. There are several fallacies in this or any other indirect method, the results being far from reliable. The pressure in the central vein of the retina is around 25 mm. Hg. A venous pulse is also observed; it is attributed to the transmission of the impulse from the artery through the intra-ocular fluid to the veins. That is to say, with each expansion of the artery the veins for a short distance proximal to where they leave the orbit are compressed and an extra quantity of blood is ejected from the eyeball.

The lens and ciliary body are described on pp. 993 and 994, the visual pathway and ocular muscles in Chapter LXXII.

THE DUPLICITY THEORY OF RETINAL FUNCTION

The theory that the retina is a duplex organ was first proposed by Schultz in 1866. There is today abundant evidence for Schultz's conception that the rods function in dim light, registering colorless-sensations only (*scotopic vision*), whereas the cones are active in bright light and are sensitive to color as well as to white light (*photopic vision*). The fovea, being composed entirely of cones, is the region where photopic vision reaches its highest state of efficiency. The surrounding (peripheral or extra-foveal) retina is composed of both rods and cones, the proportion of the former type of element increasing, that of the latter diminishing towards the periphery where cones are entirely absent.

At the risk of some repetition in other sections the evidence for the duplex nature of retinal function will be briefly reviewed.

(1) *The Purkinje shift.* When the spectrum is viewed in a bright light (i.e., by the light adapted eye, p. 968) it is seen as a series of colors with the maximum brightness (luminosity) in the yellow (sodium D-line). If the illumination of the spectrum is reduced and the eye dark adapted, the region of maximum luminosity will be found to have shifted nearer the violet end. The red portions gradually become darker, the blues correspondingly brighter, and with further reduction in the intensity of the light a point is reached where the spectrum is colorless; the maximum luminosity is now in the region of the E line (see plate 1 and fig. 398). A

Purkinje effect cannot be demonstrated at the fovea (cones only). It is evident from fig. 399 that there is no correspondence between the curve representing distribution of radiant energy in the spectrum and luminosity curves.

(2) *Evidence from the visibility curves.* In twilight vision the fovea is almost blind; vision is then mainly a function of the outlying retina which manifests enormously increased sensitivity. When the different regions of the retina are compared, it is found that the most effective wave length in causing a just perceptible sensation is 554 μ for the fovea and 510 μ for the outlying part of the retina (in testing the fovea the eye is light adapted, but is dark adapted when the peripheral retina is being examined (p. 968)). When

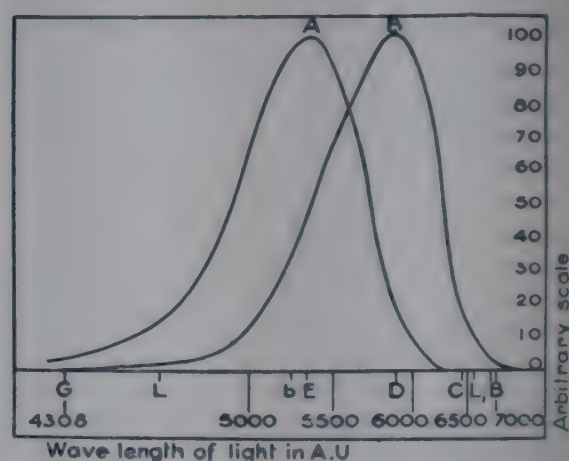


FIG. 398. Normal scotopic (A) and photopic (B) luminosity curves. (After Abney and Festing.)

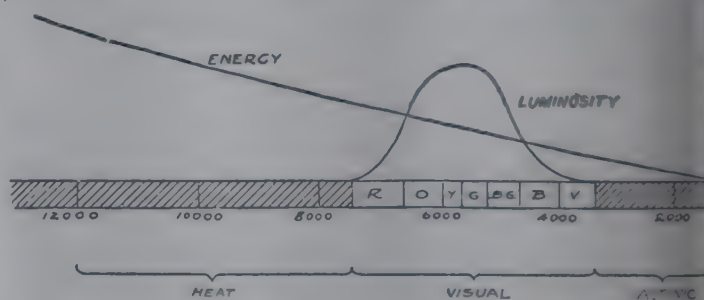


FIG. 399. Curves showing the relative energy and luminosity of the different regions of the spectrum (Starling, Principles of Human Physiology, 3rd Edition, Lea & Febiger.)

relative energy required to produce a certain sensation is plotted against the wave length the curves shown in fig. 400 are obtained. A visibility curve differs from a luminosity curve in that for its construction the actual energy values at the different wave lengths are taken into account, the energy of the light stimulus being kept constant while the wave length is varied (*equal energy spectrum*); such a curve therefore represents the variations in the sensitivity of the retina purely as a function of the wave length. Separate physical measurements (e.g., by means of a radiometer) must, of course, be made in order to determine the energy values.

(3) Using the electroretinogram (p. 973) as the criterion of retinal response Graham and Riggs found that a Purkinje effect could not be demonstrated in the white rat. The wave length of maximum effective

was the same in both the light and dark adapted eye, namely, 510 $m\mu$, which, as just stated, is that for dark adapted eye of man. The significant point is that the retina of the white rat contains only rods. In such forms as the frog and fish which possess both rods and cones the Purkinje shift can be demonstrated. On the other hand, the retinas of day birds such as the domestic hen and the pigeon, which contains cones but very few rods, show a spectral sensitivity corresponding to that of the light adapted human eye, whereas night birds such as the owl, and other mammals as well as the rat, e.g., the cat, dog and rabbit, whose retinas contain only rods, show a spectral sensitivity similar to that of the human retina in dim light.

Potential changes recorded from the human eye by the illumination of the retina with red and blue light give further evidence for photopic and scotopic mechanisms (Adrian). With red light, which

furnish additional evidence of the dual nature of retinal function.

(7) *The perception of movement* is more acute in the peripheral retina than at the fovea.

THE REACTIONS OF THE RETINA; SUBJECTIVE PHENOMENA

MECHANICAL AND ELECTRICAL STIMULATION. The visual cells—the rods and cones—are highly specialized for the reception of radiations of the visible spectrum and for the conversion of the radiant energy into nerve impulses. The retina, in the expressive phrase of Sherrington, is a “glorified heat spot.” But, though it is stimulated most effectively by light, which is therefore the *adequate stimulus*, crude visual sensations can be evoked by mechanical and electrical forms of

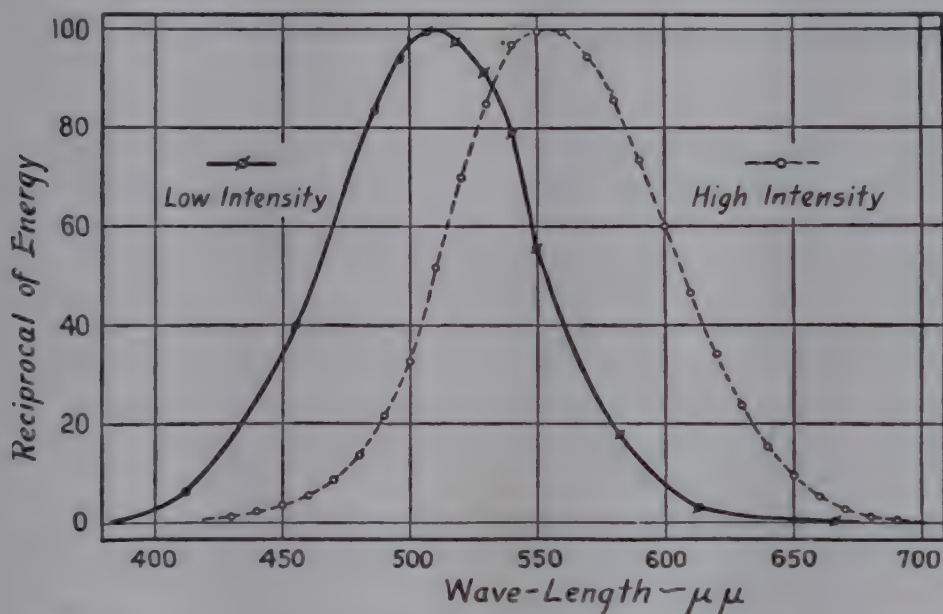


FIG. 400. Visibility curves for scotopic and photopic vision. (After Hecht.)

stimulates mainly the cones, the record shows a brief biphasic change which is increased only slightly by dark adaptation. Blue light, which stimulates the rods predominantly, results in a slower monophasic response. This response is increased greatly by dark adaptation.

(4) The sensitivity of the human retina beyond the fovea is enormously increased by dark adaptation, whereas the fovea shows relatively little change. The color sense is completely lacking from the most peripheral part of the retina which is cone-free (p. 955).

(5) *Night blindness.* In this condition, which is usually due to vitamin A deficiency but may be hereditary, vision is defective in dim lights; whereas daylight vision is normal and the spectral sensitivity of the fovea is that of the normal eye. The visual purple of the rods is lacking or regenerates very slowly in the dark after exposure to light. These facts accord with the belief in the independent function of the rods.

(6) *Visual acuity* (p. 961) and the *discrimination of light intensity* (p. 965). Investigations of these faculties and of the phenomenon of *flicker* (p. 966)

stimulation. Pressure upon the eyeball, for example, causes a luminous ring, known as a *phosphene*, to appear; and the flash of light caused by a blow upon the eye is familiar to everyone. A phosphene also results from electrical stimulation of the eyeball.

As in the case of nerve or muscle, chronaxie is a measure of retinal excitability. Verryp and Bourguignon and associates have investigated the chronaxie of the human retina, employing the phosphene response to electrical stimulation. There are apparently two chronaxies, one due to the rods, the other to the cones. With the electrodes nearer the fovea (cones) the value was from 2.1 to 2.8 σ (sigmas or milliseconds), when nearer the periphery of the retina 1.0 to 1.9 σ . The chronaxies are the same whether the eye is light or dark adapted (p. 967).

STIMULATION OF THE RETINA BY LIGHT

The wave lengths (λ) of radiant energy which stimulate the retina (visible spectrum) range from

around 320 $m\mu$ to 750 $m\mu$ (3200 to 7500 Angstrom units³). This is only about one octave of the entire energy spectrum. The last figure just given evidently represents the limit of sensitivity of the retina to the longer wave lengths, for the media of the eye will transmit infra-red rays up to λ 20,000 $m\mu$. On the other hand, the absolute limit of transmissibility of the shorter waves is about 320 $m\mu$; this figure applies only if the illumination is intense and even then few under 400 $m\mu$ reach the retina. The failure of the retina to respond to rays of waves of shorter length than this is apparently because the ocular media are opaque to them.⁴

The cornea transmits rays from λ 297 $m\mu$ to λ 20,000 $m\mu$ though the transmission above λ 17,000 $m\mu$ is small (2 to 20 per cent). Of the rays reaching it, the lens transmits only a small proportion of those below λ 400 $m\mu$ or above λ 13,500 $m\mu$, and none below λ 300 $m\mu$. That is to say most of the rays between λ 400 $m\mu$ and λ 297 $m\mu$ are absorbed by either the cornea or the lens. Wave lengths between 350 $m\mu$ and 400 $m\mu$ cause fluorescence in the lens. The phenomenon of fluorescence, in general, is attributed to the transference of the energy of the incident radiations to particles of the substance absorbing them. The particles then act as independent light sources, emitting waves which are, for the most part, longer than the original radiation. Thus, the lens converts the harmful shorter waves to longer ones which are permitted to reach the retina. That wave lengths shorter than those which are transmitted by the lens are capable of stimulating the retina is shown by the fact that the visible spectrum is extended towards the blue end after removal of a lens of normal transparency. In old age, on the other hand, the lens becomes more opaque; the upper limit of visibility is around λ 400 $m\mu$ and in the early stages of, the cataractous lens (p. 998) the upper limit is raised to λ 440 $m\mu$.

The quantity of light energy⁵ necessary to simulate the retina is not constant for all wave lengths

$$^3 m\mu \text{ or millimicron} = \frac{1}{1,000,000} \text{ mm.}; \text{ an Angstrom unit (A.U.)} = \frac{1}{10,000,000} \text{ mm.}$$

⁴ The X-rays, of course, penetrate the eye and to such the retina is sensitive. This may be demonstrated by means of metal letters or figures placed in front of a normal eye with closed lids or before any eye in which the retina is normal. A word can be read in this way; the letters when exposed to the rays are clearly recognized as shadows (not images) against a bright ground. The rays are not refracted and the shadows are not inverted upon the retina; therefore, if they are to appear upright to the subject they must be placed in the reverse position in front of the eye (see p. 987).

⁵ Radiant energy is expressed in *ergs*. The erg is a purely objective or physical unit, being quite independent of visual sensations. The energy is measured by

of the visible spectrum. In the dark adapted eye the energy required to stimulate the rods and cause a just perceptible sensation is least for green light with a wave length of about 507 $m\mu$ (see p. 967) and has been estimated by Hecht at from 2.2 to 5.7×10^{-10} ergs⁶, measured at the surface of the cornea in the dark adapted eye. This equals from 58 to 148 quanta of light. After allowance was made for loss of energy in transmission to the retina through the ocular media and for incomplete absorption by the rods, the value was only from 5 to 14 quanta or one quantum absorbed per stimulated rod. The extraordinary sensitivity of the retina to light may be expressed in simpler terms by saying that light emitted by a standard candle at a distance of nearly a mile would be visible if the air were perfectly transparent. Such examples indicate that the eye has a sensitivity some 300,000 times greater than that of the

means of a thermopile, bolometer or radiometer. The *meter candle* is a unit which is in part subjective and in part objective. It is a measure of surface illumination, being defined as the light *incident* per second per sq. cm. of a surface placed at right angles to the beams from a standard (international) candle 1 meter distant (a standard candle is made of spermaceti, weighs $\frac{1}{4}$ lb. and burns 120 grains of wax per hour with a flame 45 mm. high). Illumination is measured by means of a photometer. If, for example, the illumination of a lamp is to be measured, a photometer is set up at this point, and a standard candle is moved until its light just matches that of the lamp. If the candle's distance

in meters is d , then the surface illumination is $\frac{1}{d^2}$. The meter candle is thus a measure of the visual stimulus, not of the sensation itself. The quantity of light *reflected* from a perfectly diffusing surface (e.g., of magnesium oxide) illuminated by 10,000 meter candles is termed a *lambert* (l); a millilambert (ml) is $\frac{1}{1000}$ lambert. The *lumen* is the unit of *emitted* light (*luminous flux*). One lumen is the light emitted in a *unit of solid angle* by a uniform point source of 1 standard candle. A point source is regarded as occupying the center of a sphere; a unit solid angle is the angle subtended at the center of the sphere by an area on its surface equal to the square of the radius. The area of a sphere is $4\pi r^2$, therefore 1 standard candle emits 4π lumens. The intensity of a light source is expressed in lumens, i.e., the luminous flux emitted in any direction per unit of solid angle.

The *photon* is the unit of the *sensation of brightness*. The brightness of an object to the eye depends not only upon the light which it reflects, but also upon the quantity of light which enters the eye, i.e., upon the brightness of its retinal image and upon the state of the retina, whether dark or light adapted (p. 967). The brightness of the image varies, of course, with the diameter of the pupil. A photon is therefore defined as the light in millilamberts multiplied by the area of the pupil in sq. mm. For example, if the illumination of an object is 10 ml and the diameter of the pupil 6 mm. (area = $\pi r^2 = 3.14 \times 9 = 28.26$ sq. mm.) then the brightness is ($28.26 \times 10 =$) 282.6 photons.

⁶ The quantum of green light is 3.84×10^{-18} ergs.

most delicate radiometer and about 3000 times greater than that of a rapid photographic film. The minimum quantity of light energy required to evoke a visual sensation increases progressively towards either end of the spectrum, being several thousand times greater for red and blue than for green light.

The quantity of light energy, i.e., the intensity of the light in the physical sense, required to cause a just perceptible sensation—the *intensity threshold*—is therefore a function of the wave length. The sensitivity also varies in different regions of the retina (p. 956) with the state of adaptation of the eye (p. 967) and with the illumination of the surrounding field.

The intensity threshold is influenced by two other factors, (a) the duration of the stimulus and (b) its extensity, i.e., the size of the light source. At the threshold, the product of intensity, duration and extensity is constant within limits. For example, if a light of a given intensity and size and acting for a given length of time is just below the threshold of visibility, it is perceived upon raising the value of any one of these factors. Or if a light of a certain intensity, duration and size is just visible it becomes invisible if one of these factors is reduced. The relationship between intensity and area (*intensity* \times *area* = *constant*) is known as Ricco's law.

Anyone who has used a camera will recognize that in respect to the relationship between intensity and duration the retina behaves like a photographic film—the lower the illumination the longer must be the exposure, and vice versa. As a matter of fact, the retina obeys the Bunsen-Roscoe law applicable to photosensitive reactions in general (*intensity* \times *time* = *constant*). In the case of the retina this relationship holds only for periods of less than about $\frac{1}{2}$ of a second. Also, the relationship between intensity and area is valid only for retinal areas under about 0.8 sq. mm. It would appear from the foregoing considerations that the total quantity of light energy falling upon the retina within a given time is the fundamental factor which determines the retinal response.

The smallest area which can be perceived is called the *minimum visible*. The angle subtended at the nodal point of the eye by the minimum visible is referred to as the *minimum visible angle*. But from what has been said it is quite evident that neither of these can be given any absolute value. A light could be reduced in size indefinitely to a mathematical point—and, provided it were

sufficiently intense, would still be visible; a star, for example, subtends an infinitesimal visual angle.

VISUAL ACUTY, THE RESOLVING POWER OF THE EYE. The acuteness of vision (or visual acuity) is dependent upon several retinal functions, e.g., the sensitivity to light (intensity threshold), the minimum visible and the ability to recognize the separateness of two closely approximated points or parallel lines. The threshold of the latter faculty is commonly referred to as the *minimum separable*¹ or the *resolution threshold*. Visual acuity is the basis of the *form sense*, by which is meant the power of determining by sight the shape, form, outline and minute detail of our surroundings. Visual acuity is customarily expressed in terms of the minimum separable or, to be more explicit, as the reciprocal of the angle subtended at the nodal point of the eye—the *visual angle*—by the space

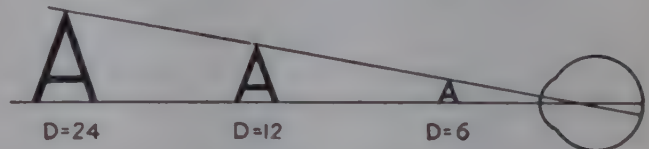


FIG. 401. See text.

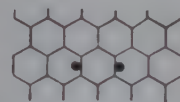


FIG. 402. See text.

between two objects situated at the minimum distance apart at which their duality can be recognized. For example, if the visual angle is 1.321 minute, then the visual acuity is ($\frac{1}{1.321}$ =) 0.756. The average normal eye can resolve two points when the visual angle is 1 minute (60 seconds). The minimum angle that has been reported is 44 seconds (vis. ac. 1.492). As an object is moved away from the eye its visual angle becomes progressively smaller. Consequently, those details of form and structure which subtend an angle of a minute or more at the nearer point and are therefore visible, gradually become imperceptible with increasing distance. In other words, in order to see an object at a distance as clearly as when it is near the eye, it would need to be increased proportionately in size (see fig. 401).

In determining the visual acuity figures such as the broken circle **C** of Landolt or Snellen's prong, **E**, painted black on a white ground and in graded sizes are employed. The subject is seated at a distance of 6 meters (20 feet) and a figure is placed with the gap

¹ The minimum separable is analogous to two point discrimination in cutaneous sensation (p. 800).

of the **C** or the prongs of the **E** turned to the right or left; he is asked to say in which position the figure is directed. The width of the lines composing the figures and the gap in the **C**, or the spaces between the prongs of the **E**, subtend angles of various degrees, depending on the size of the figure, when placed at a distance of 6 meters. The width of the whole figure is five times that of its parts. By finding the smallest figure whose position can be recognized the visual acuity of the subject (in terms of the visual angle) is ascertained. In testing the visual acuity for the fitting of glasses Snellen's *test type* is most commonly employed. This test is devised upon the basis that two points or lines separated by a space having a visual angle of 1 minute can be resolved by the average normal eye. The test type comprises nine rows of block letters printed in black upon a white card. The rows are arranged in descending order of size from above down. The width of the lines forming the letters of the first row subtends an angle of 1 minute at 60 meters from the eye, while that of the letters in the other rows, two to nine, have a visual angle of 1 minute at 36, 24, 18, 12, 9, 6, 5 and 4 meters, respectively. The card is placed in a good light, the patient is seated facing it at a distance of 6 meters and asked to read down as many rows as he can. The visual acuity is expressed as a fraction, the numerator being the distance at which the subject is seated from the card and the denominator the distance at which the letters could be read by the normal eye. Thus, if he reads the seventh row of letters, i.e., those with a visual angle of 1 minute at 6 meters his vision is $\frac{6}{7}$ or normal. If, on the other hand, he can see distinctly only as far as the fourth row, which the normal eye can read at 18 meters, his vision is $\frac{6}{18}$; if as far as the third row his vision is $\frac{6}{24}$, and so on, for any other row which he is just able to read.

Knowing the distance of the nodal point of the eye from the retina and the visual angle, the size of the retinal image of an object can be calculated (p. 988). With a visual angle of 1 minute the space on the retina separating two point images is 4.4μ . The diameter of a foveal cone is given by different observers as between 2.5 and 4.0μ . Even if the higher of these figures is taken, then the image of two dots separated by 4.4μ would fall upon two cones separated by a single unstimulated cone or by one stimulated differently, i.e., by the image of the interspace (fig. 402).

From such calculations it has been argued that cone diameter is the limiting factor in discriminating two points or thin lines, for obviously with an interspace less than a cone width the two dots would fall upon a single cell, and from what is known of the nerve impulse it cannot be admitted that two parts of a visual receptor upon receiving simultaneously different types of stimulus can give rise to dissimilar sensations.

Difficulties stand in the way of so simple an explanation. The eyes, even with the most exact fixation,

are constantly executing fine movements, a fact which precludes the possibility that the retinal image stimulates any set pattern of cones; the image must be constantly shifting its position. This theory must make the assumption that when the angular distance separating two objects is about the diameter of a cone the two images must be dodged about with almost incredible precision, so that they come to lie not adjacent cones (see fig. 402) but on two cones separated by an unstimulated cone or by one stimulated differently. Adler concluded from his experiments, in which fixation as exact as possible was secured, that a point image moves over from 2 to 4 cones at least. Furthermore, the size of the image on the retina cannot, owing to the diffusion of light, be calculated with the precision implied by the foregoing calculations (see below). It is true that the smallest visual angle recorded ($44''$) for a space between two visually discrete objects would give a retinal image larger (3.2μ in diameter) than some of the estimations (3.0μ) of cone diameter—a fact which fits the theory that the latter is the limiting factor. Nevertheless, it is probable that the correlation is more than a coincidence.

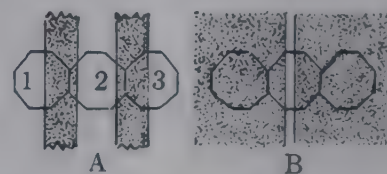


FIG. 403. Description in text.

Wilcox and Purdy suggest that the essential factor is the total illumination of the central cone as compared with its fellow on either side. Thus, in fig. 403 A, cone 2 receives more light than cones 1 and 3. There is a reason then theoretically why the interspace separating two lines could not be narrower than the width of a single cone and still be recognizable. A limit would be reached, however, when the white interspace was reduced to about half the width of a cone; then all three cones must be illuminated equally. It may be asked, what essential difference is there between the minimum visible (p. 961) and the minimum separable? That the minimum visual angle should be so much greater in the one instance than in the other? Two parallel black lines upon a white surface are recognized as separate because a third white line is seen between them. Why then, provided it is bright enough can it not be seen, even though reduced to an almost infinitesimal width? The difference in the two instances appear to be a matter of the background and may be illustrated by fig. 403 B. A bright light upon an extensive background illuminates a single row of cones while all cones for a distance on either side are unilluminated. According therefore to the conception of Wilcox and Purdy, no difference exists, in so far as the fundamental retinal process is concerned, between the minimum visible and the minimum separable.

As with other faculties of the eye, no absolute and constant value can be given for the minimum separable. It varies greatly with several factors, viz., (a) the *intensity of illumination* of the test object, (b) the spectral character of the light, (c) the region of the retina stimulated and (d) the size of the pupil.

The resolving power of the eye for two points increases with the illumination, as illustrated in fig. 404. This is a fact difficult to explain. It might be thought that as long as the illumination was above the threshold for a just perceptible sensation, increase in the intensity of the light would be without influence upon the threshold for the minimum separable. Two theories which have been proposed to account for the phenomenon

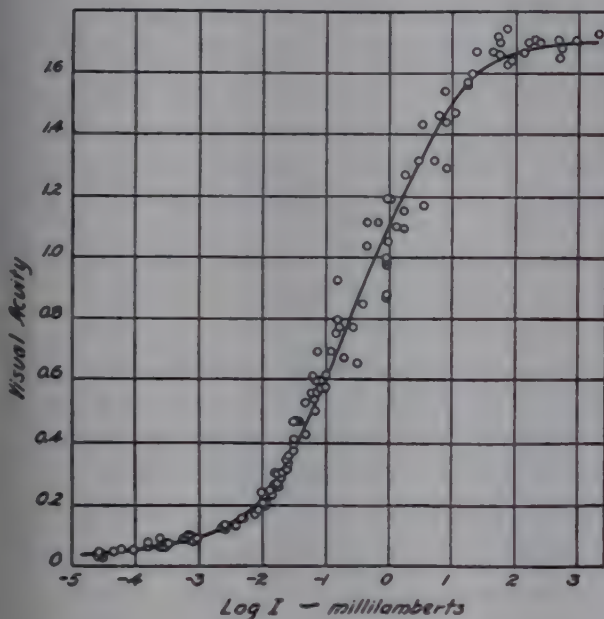


FIG. 404. Relation between visual acuity and illumination. (After Hecht.)

will be mentioned, not because they give any final answer to the problem, but because they bring up some interesting points.

Hartridge proposes a theory based upon the aberrations of the optical system of the eye and the ability of the retina to discriminate between small differences of light intensity (p. 964). The retinal image is not clearly defined but is blurred by diffusion circles or bands, due to the diffraction of light at the pupillary margin and to colored fringes (chromatic aberration, p. 1000). Assuming the pupil to be 3 mm. in diameter and a foveal cone 3.2 mm. across, he made the following calculations of the light distribution on the retina caused by a white line separating two dark areas. The illumination of the row of cones corresponding to the center of the line image was taken as 100. The illumination of the next row was 31%, of the next 9%. The diffusion bands thus virtually increase the width of the image of the white line beyond that indicated by calculations from the visual angle, and encroach upon

the dark boundaries. The fine movements of the eyes are continually shifting the image and even the slightest movement will cause the line of junction between the outermost diffusion band and the dark area to move from one row of cones to another. A row of cones is therefore stimulated at one instant at a different intensity than at the next. If the difference in light intensity is greater than 10% it is appreciated, and thus a gap between the two dark areas is detected. Now the threshold for discrimination of differences in light intensity varies with the illumination (p. 965). Consequently, when the illumination is reduced the difference between the intensity of the outermost diffusion bands and of the dark areas is not perceived, i.e., the shift of the line of junction from one cone to the next causes no sensation. The difference between the illumination of the inner and outer bands may be still detectable, but the width of the bright line will be re-

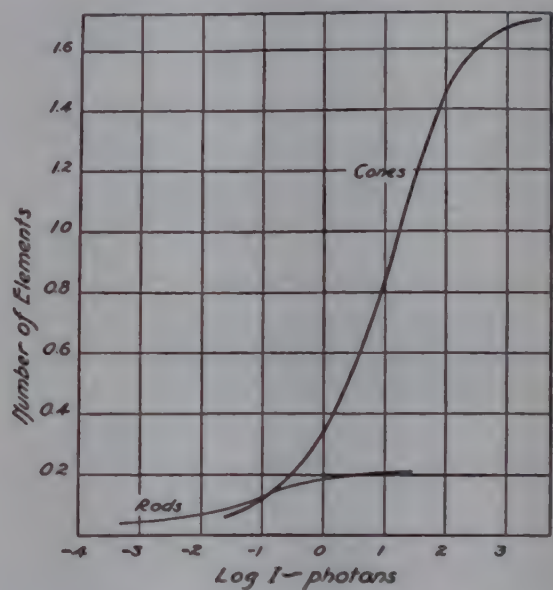


FIG. 405. Statistical distribution of sensibility of rods and cones. The ordinates read directly in units of visual acuity. (After Hecht.)

duced. With further reduction in the illumination and the consequent raising of the threshold for intensity discrimination the white image becomes still narrower and finally, when the angular width is about 1", the dark areas fuse across it.

Hecht's theory postulates a change in the "grain" of the retina as a result of variations in illumination. The retina, according to Hecht, is made up of sensitive elements of different intensity thresholds distributed in a statistical manner similar to that of other populations. At low levels of illumination only a proportion of these elements (i.e., rods with the lowest threshold) are excited. The active elements are therefore farther apart and the "grain" of the sensitive surface is relatively coarse. As the light intensity increases the thresholds of more and more elements are exceeded. More rods function, that is, the number of active elements is increased and the "grain" of the retina is finer. As the illumination rises further, cones, first those with the lowest thresholds and later less sensitive ones, become active. The maximal effect of increasing the illumina-

tion upon the resolving power is reached when the entire rod and cone population is responding (see fig. 405). Objections to both of the theories just outlined could be cited; several observations indicate that the threshold for the minimum separable is not dependent entirely upon retinal factors but that central processes play an important part.

The resolving power of the eye is greater for monochromatic light than for a mixed light source such as daylight when the two have equal illuminating values. This fact is due to the absence of chromatic aberration in the former instance. Monochromatic yellow light (575 $m\mu$) gives the highest value, next in order come green, red and blue. Mercury arc light, owing to its greater homogeneity, gives higher values than ordinary white light.

Three factors are involved in the effect of pupillary size upon the resolving power of the retina. Increase in diameter allows more light to enter the eye and therefore increases the illumination of the retinal image and raises the visual acuity. Diffraction

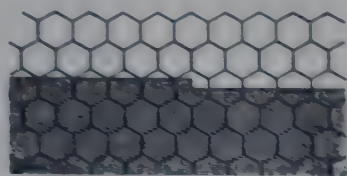


FIG. 406. (After Adler.) See text.

tion is also reduced by widening the pupillary aperture which will tend to improve the definition of the image. On the other hand, narrowing the pupil diminishes chromatic aberration. The optimum pupillary size lies between maximum constriction and full dilatation, namely, at a diameter of about 3 mm.

With ordinary illuminations the visual acuity is some twenty times greater at the fovea than in any outlying part of the retina. In the dark adapted eye (p. 967) the peripheral retina has a much higher value than the fovea.

The illumination of the field surrounding the test object (the surrounds) has an important influence upon the resolving power of the eye. A uniform increase in the illumination of the surrounds up to $\frac{1}{10}$ that of the test object progressively increases visual acuity. Raising the illumination of the surrounds from this point to equality with the test object causes a slight reduction in visual acuity and, when the surrounds become brighter than the test object, there is a decided depression. A very bright but small light source situated in the neighborhood of the test object, e.g., a motor head light, causes a very marked lowering of the visual acuity. The effects caused by such concentrated

sources of light are referred to as "glare." If the surrounding light source is not too bright and especially if the surrounds are dark, little depressing effect upon the acuity of vision is produced, indeed there may be an improvement due to the accompanying pupillary constriction.

THE DISPLACEMENT THRESHOLD OR THE VERNIER ACUITY. These terms are applied to the visual faculty of recognizing a break in the continuity of a border, a variation in width of a line or the lack of alignment of two straight lines placed end to end. This power of the eye is some ten times greater than its ability to resolve two points. A break in a line subtending an angle as small as $5''$ or even $1''$ can be detected under optimal conditions. It seems quite certain that this visual faculty is not limited by cone diameter, for the break must lie on a single cone, and the lines on both sides of the break on the same row of cones (fig. 406). It is probable that the underlying mechanism is different from that governing the threshold for the discrimination of two points. For example, its threshold is only slightly raised by increasing the illumination (p. 963).

Anderson and Weymouth offer an interesting theory to account for the extraordinary accuracy of the vernier acuity. They suggest that the slight but continuous eye movements shift the line image over the retina, causing successive stimulus patterns. The averaging of the successive patterns gives a sense of position which they call *retinal local sign*. The longer the lines, the greater are the number of patterns presented to consciousness and, consequently, the more accurate is the averaging process. For details of the view of the authors the reader is referred to their original paper.

SOME PRACTICAL CONSIDERATIONS WITH REGARD TO LIGHTING. Besides reducing visual acuity, glare causes discomfort and one instinctively attempts to protect the eyes by closing the lids, raising the hand as a shield; the pupil constricts. A constant source of glare, even of mild degree, results in eye strain. Glare has been classified into three types—veiling, dazzling and blinding. *Veiling glare* is that due to strong light which, being uniformly superimposed upon the retinal image, reduces contrast. The light reflected from a printed page under a bright sky is an example. *Dazzling glare* is due to scattered light in the ocular media which does not form part of the retinal image (p. 1000). Such can be produced by a strong light shining into the eye from an angle of about 45° . *Blinding glare* results when one looks

directly at a very bright light. It is due to an actual reduction of retinal sensitivity.

For moderately fine work, such as reading, sewing, typesetting, etc., the illumination of the objects should not be less than from 10 to 20 foot candles. An illumination of 10 foot candles is efficient for reading ordinary black type on good paper, but the higher illumination is necessary if the printing or the paper is of poor quality. The effect of lighting upon the performance of typewriters, mail sorters and others engaged in fine work has been the subject of a number of investigations. Raising the illumination has been found to increase the rapidity and accuracy of the work from 10 to 16 per cent and to reduce eye strain and general fatigue. The maximum efficiency appears to be reached when the illumination is about 20 foot candles. The lighting should be diffuse, and naked bright light sources which would cause glare eliminated. The central field should receive additional lighting so that its illumination will be from 5 to 10 times that of the surrounds. The constant use of the eyes in poor lighting leads to ocular strain and fatigue with consequent headache. It may cause increase in pulse rate and even nausea; ultimately serious eye defects, especially in the young, may result. The quality of the light is also an important factor. Nitrogen light, being more homogeneous, has a higher visual acuity than the ordinary incandescent light bulb; the kerosene lamp lies between the two.

THE DISCRIMINATION OF DIFFERENCES IN LIGHT INTENSITY. This faculty was first investigated by Bouguer in 1760 and later by Weber (1834) and Fechner (1858). The latter observer found that when the light intensity is gradually increased the least change in illumination which can be perceived by the subject occurs in a series of steps. This relationship is expressed in the Weber-Fechner law which is applicable not only to vision but to other senses as well. The law states that the least perceptible difference between a series of stimuli is in each instance a certain constant fraction of the preceding stimulus. For example, let us suppose that for vision the constant is $\frac{1}{100}$ and the initial illumination is 100 candles. Then, if the light of one more candle is added, the difference in illumination will not be recognized; that is, the light of 101 candles is perceived to be greater than that of 100. If we were 1000 candles to start with, 10 more would need to be added before any difference could be noticed. If, therefore, the logarithms of the

intensities are plotted (abscissae) against the least perceptible differences in sensation (ordinates) a straight line should result. The law may be stated in another way, namely, that in order to cause a series of equal increments in sensation the strength of the stimulus must increase in geometrical proportion. Or again, the added intensity (ΔI) necessary to cause a just perceptible difference in sensation (ΔS) bears a constant ratio $\left(\frac{\Delta I}{I}\right)$ to the preceding intensity (I). Thus, $\Delta S = K \frac{\Delta I}{I}$.

When the logarithms of the light intensity are plotted against the just perceptible differences, the curve shown in fig. 407 is obtained. The curve is composed of three parts. It is only section A representing the relationship at moderate light intensities that accords even

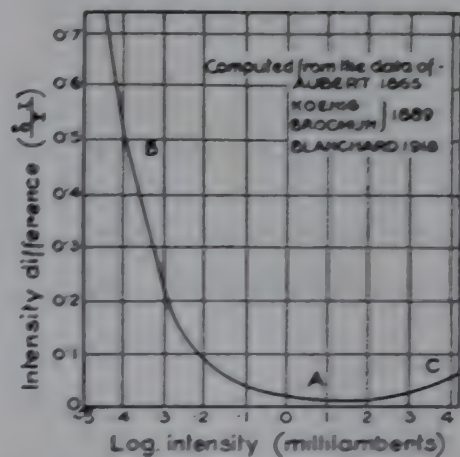


FIG. 407. Curve of the intensity discrimination of light. (After Hecht.)

approximately with the Weber-Fechner law. At intensities below and above this limited range marked deviations from the law occur (sections B and C). The whole curve covers a range from the lowest intensity to one of dazzling strength and comprises 572 steps of just perceptible differences. Starting with the very lowest intensities, e.g., 0.0000484 millilamberts (I) the least absolute increment of the stimulus which is effective (ΔI) is very small (Koenig and Brodhun's data), namely, 0.0000316 millilamberts, and increases progressively as the intensity rises, so that at an illumination of 3.853 ml ΔI has a value of 147.0 ml. The fraction $\frac{\Delta I}{I}$, therefore, is not constant, nor does it show a continuous change in one direction, for it diminishes from about $\frac{1}{100}$ at the lowest intensity to about $\frac{1}{1000}$ at moderate ranges and then rises again to $\frac{1}{100}$ at the highest intensity.* Hecht considers that the low intensity part of the curve (B) represents rod func-

* Some recent observations indicate that this increase with higher intensities does not occur if the eye is fully light adapted, the fraction remaining at the lowest value even though the illumination is unpleasantly intense (see Craik).

tion and the high intensity portion (C), the activity of the cones. The cones are therefore more sensitive to *differences* in illumination than the rods, though their threshold for light perception (intensity threshold) is higher (p. 961).

INTERMITTENT RETINAL STIMULATION; FLICKER.

When the retina is stimulated intermittently by a series of light flashes as may be produced by interrupting a continuous light by a rotating notched disc or by reflecting light from a rotating disc divided into alternate black and white sectors, a characteristic flickering or unpleasant glittering sensation is experienced when the periodic stimulation reaches a certain frequency. Upon further increasing the speed of rotation and, in consequence, the frequency (number per second) of the light stimuli, fusion results and the flicker disappears to be replaced by a continuous sensation. The frequency at which this occurs is called the *critical fusion frequency* (C.F.F.). If the duration of the flashes at the instant of fusion be designated a and the length of the dark intervals between them designated b then the sensation produced is equal to that which would result from a continuous stimulus having the value $\frac{a}{a+b}$. This is known

as the Talbot-Plateau law. It accounts for the well-known fact that a gray sensation of any depth can be matched by throwing black and white images alternately and at a suitable frequency upon the retina. Similarly white and red images give, at the critical fusion frequency, a sensation of pink, blue and red a sensation of purple, yellow and green of yellowish green, and so on. These effects are simply explained by *visual persistence*, that is, the sensation evoked by one image has not passed off before the next one is produced, thus a blend of the two sensations in consciousness results.

The value of the C.F.F. is variable, depending upon several conditions the most influential of which is the intensity of the light, the value rising as the intensity increases. The influence of light intensity is embodied in the Ferry (1892)-Porter (1906) law which states that the *critical fusion frequency is directly proportional to the logarithm of the light intensity*. Thus $n = K \log I$,⁹ where n = flashes per second and I = illumination.

⁹ Determination of the C.F.F. furnishes an accurate and convenient method for comparing the brightness of differently colored lights. It is especially valuable in the comparison of the brightness of colored lights because of our natural tendency to confuse the brightness of a color with its hue or saturation.

The Ferry-Porter law is valid, however, only under certain special conditions; it holds over moderate ranges of illumination of the test object when the image is restricted to the fovea. Above and below this middle range the linear relationship between intensity and the critical fusion frequency does not hold. Porter, using a test object whose image fell upon the fovea and upon the surrounding retina as well, found that the intensity-C.F.F. relationship could be expressed by the formula $n = K \log I \times K^1$; the value of K is different for high and low levels of illumination. When the value of n is plotted against $\log I$ at low and at high intensities the points fall on two straight lines, one at low the other at high intensities. It is believed that these represent respectively rod and cone function, a conception borne out by the results of Hecht and associates and of Lythgoe and Tansley.

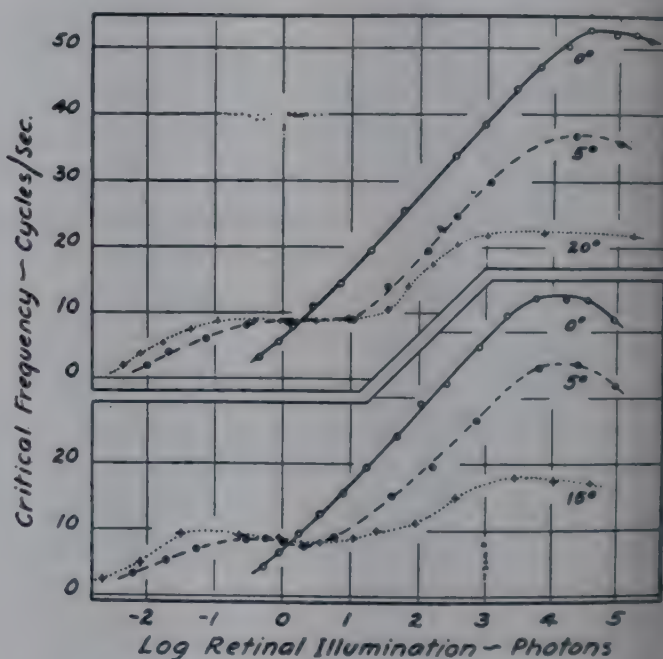


FIG. 408. Relation between critical frequency and $\log I$ for white light with a 2° field in four retinal locations; at the fovea, and at 5°, 15°, and 20° above the fovea. (After Hecht from Hecht and Verrijp.)

Hecht found that with a stimulus restricted to the fovea (cones) the relationship was linear for a middle range of illumination, but above this the curve flattened out; below, it formed a very gentle curve. With the image on extra-foveal regions the data form two intersecting straight lines, one at lower the other at higher intensities, the former presumably represents rod function, the latter peripheral cone function (fig. 408).

Lythgoe and Tansley observed that during dark adaptation the C.F.F. falls in both the fovea and the peripheral parts of the retina when the intensity of the test light was high (6.8 foot candles). At low intensities (0.020 foot candles) the C.F.F. also falls at the fovea, but rises in the peripheral retina. Now, as judged by other criteria, only cones are functioning at high intensities whether the fovea or the peripheral retina is being tested; at low intensities only rods. Also, it was found by Lythgoe and Tansley that when red light was used for testing (rods insensitive), and

a case of night blindness (defective rods) a fall in the value of the C.F.F. occurs during dark adaptation. The fall in the value with high illuminations of the test object is due presumably to the cones and the rise with low illuminations to the rods. At moderate illuminations of the test object a fall occurs during the first 5 minutes of dark adaptation (due to cones), see p. 958 followed by a rise (due to rods). The critical frequency due to the rods is highest with dark surrounds; that due to cones is increased by bright surrounds, the maximum being reached when the brightness of the latter and of the test object are equal.

A study of the retinal potentials (p. 973) during intermittent stimulation shows that when a light flash falls upon the retina during the "off effect" of a preceding stimulus, the *d* wave is interrupted and a pronounced negative dip occurs. This is an exaggerated *a* deflection (P_{III}). The negative deflection is followed by a large positive swing which, if the second stimulus occurs soon after the first, is simply the return of the momentarily interrupted "off effect" of the first. If the interval between the two is greater, the upswing

- (1) Dilatation of the pupil.
- (2) Increased sensitivity of the retina, i.e., lowering of the intensity threshold and of the thresholds for the minimum separable and the discrimination of intensity differences.
- (3) Purkinje shift (p. 958) towards the blue end of the spectrum.
- (4) Regeneration of visual purple in the rods.
- (5) Certain structural alterations in the retina (of cold-blooded animals) and a change in reaction from acid to alkaline (see p. 973).

In bright illumination the pupillary diameter is about 3 mm., but when the eye is shielded from light the pupil immediately commences to dilate and reaches a diameter of 8 or 9 mm. in full dark adaptation. In the dark adapted eye the first detectable response—slight constriction—of the pupil occurs at an illumination of about 0.025 meter candles.

The intensity threshold of the peripheral retina

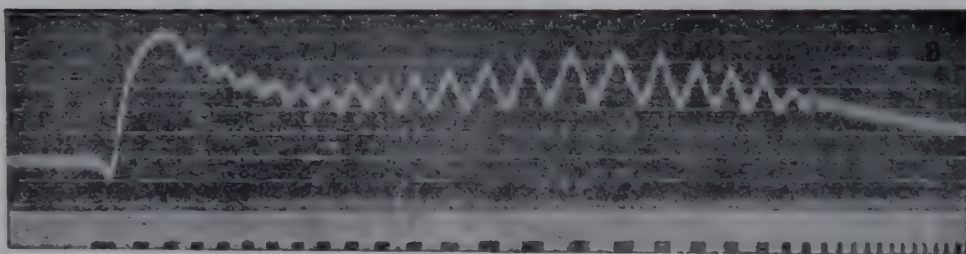


FIG. 409. Electroretinogram recorded during intermittent stimulation. See text. (From Granit.)

is higher, and is then due to the *b* deflection (P_{II}) of the after coming stimulus. Thus, if the light flashes are so timed that each interrupts the "off effect" of its predecessor, a series of regular ripples appears in the electroretinogram which apparently are the cause of the flickering sensation (fig. 409). No negative dip occurs nor do the characteristic ripples appear if a flash falls upon the retina *before* the "off effect" of the preceding one—a continuous sensation should therefore result.

ADAPTATION OF THE EYE TO DIFFERENT LIGHT INTENSITIES

The retina behaves differently in partial darkness than in bright light. It has been pointed out elsewhere (p. 958) that this difference is attributed to the independent functions of the rods and cones.

DARK ADAPTATION. SCOTOPIC VISION. The phenomenon was first studied by Aubert in 1865. It is common experience that upon passing from light into darkness we become blind for the moment; but soon a faint glimmer of light appears and gradually more and more of the detail of our surroundings becomes visible. The adaptation of the eye to the low illumination is associated with the following changes.

commences to fall almost upon the instant that the eye is darkened, the fall being very rapid for the first 10 minutes. After this and up to 30 minutes, the fall in the threshold is less precipitous and from then on is very slow. For practical purposes the extrafoveal retina may be considered to have reached its maximum sensitivity after about 40 minutes in the dark, though a gradual slight increase occurs for several hours thereafter. The light sensitivity of the peripheral retina is increased by from 10,000 to 20,000 times by dark adaptation (fig. 410).

It has been doubted that dark adaptation of the fovea occurs; this is now conceded though it is of minor degree. When the eye is fully dark adapted the sensitivity of the fovea is only about $\frac{1}{1000}$ that of the extrafoveal retina. It is a familiar fact that in partial darkness an object may be seen "out of the corner of the eye" (peripheral vision) but is invisible when the eyes are turned to look directly at it (foveal vision). Foveal dark adaptation is very rapid, being almost complete within from 3 to 4 minutes. Hecht found that a small red cross (wave length greater than 650 m μ), to

which the rods are almost insensitive, was seen at a much lower threshold of illumination by the dark adapted eye. The threshold was found to fall from 450×10^{-4} ml. to 10×10^{-4} ml. in 30 seconds and to 3×10^{-4} in 20 minutes.

The color sense in the dark adapted eye. The rods are insensitive to color, and in the dark adapted eye their threshold to white light is very much lower than that of the fovea; therefore, a colored object with an illumination value around the threshold of the rods first appears without color. As the illumination of the object is increased its color is perceived when the threshold of the cones is reached. The interval between the two thresholds is called the *colorless (achromatic) interval*. There is no colorless interval for red, since the rods (like the photographic film) are insensitive to this color (λ greater than $650 \text{ m}\mu$). In other words a red object appears black in a very dim light and is detected with difficulty against a dark background; not until the intensity of its illumination reaches the threshold of the cones is it perceived. In red light, therefore, dark adaptation of the rods is not prevented. The achromatic interval is shortest for blue. In severe instances of night blindness the Purkinje shift and the achromatic interval for all wave lengths are absent; this is what one would expect to result from the rod defect.

LIGHT ADAPTATION. PHOTOPIC VISION. The dark adapted eye is dazzled by even moderately bright light, but adaptation to the higher illumination develops rapidly. During light adaptation changes opposite in nature to those occurring in darkness take place, namely,

- (1) Constriction of the pupil.
- (2) Diminished sensitivity of the retina.
- (3) Purkinje shift towards the red end of the spectrum.
- (4) Bleaching of visual purple.
- (5) Shift in reaction of the retina from alkaline to acid and structural changes, in certain species (p. 973).

The eye adapts much more readily to light than to darkness. In its measurement the threshold at full adaptation is first determined; the eye is then exposed to bright light for a certain period after which the light is switched off and the threshold found before any appreciable degree of dark adaptation has developed. This procedure is repeated for different time intervals following the preliminary period of dark adaptation. It is found that the greatest decrease in sensitivity occurs during the first 20 or 30 seconds; this is followed by a gradual fall for a period of 10 minutes. After this time light adaptation may be taken for practical

purposes to be complete, though some slight reduction in sensitivity occurs up to 30 minutes.

THE PERCEPTION OF MOVEMENT. This is the most primitive of the visual functions; in disease it is the last to fail and is the first to return should any improvement in vision occur. The peripheral (extrafoveal) retina is a specially differentiated organ for the perception of movement (Exner), being much more sensitive in this respect than the fovea. It is a familiar fact that a slight movement is more readily detected if the moving object

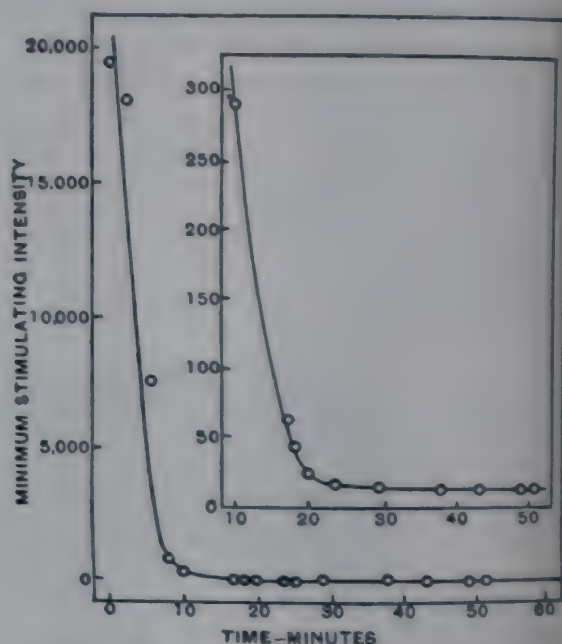


FIG. 410. The course of dark adaptation. The lower portion of the curve is redrawn in the inset on a magnified scale of ordinates. The exceedingly great change in the intensity during the first 10 minutes is clearly seen. (After Hecht, *J. Gen. Physiol.* 1922, 503.)



FIG. 411. Illustrating irradiation.

is not in the direct line of vision, i.e., when the image falls upon the peripheral retina, than when the eyes are fixed upon it. The most sensitive part of the retina is from 10° to 15° from the fovea but diminishes progressively towards the periphery. In the region of maximum sensitivity the angular velocity of a just perceptible movement is from one half to one minute per second, provided that there are stationary objects in the visual field to serve as reference points. When such are absent the angular velocity must

from 10 to 20 times as great in order for the movement to be perceived. On the other hand, if the angular velocity is very great the movement is not perceived; owing to visual persistence a very rapidly moving object appears as a stationary streak. The total distance travelled, i.e., the displacement of the object, as well as the angular velocity is, of course, a factor in movement perception. The minimum displacement is about 17 seconds of arc, under optimal conditions. The sensitivity of the retina to movement is lower in the dark adapted than in the light adapted eye.

When the eyes are stationary but the body or head is moved an *apparent* movement is given to objects in the visual field. When travelling in a train, for example, near objects appear to move in the opposite direction to the direction of travel, while those in the background appear to move with the moving vehicle. Apparent movements of surrounding objects also occur when the eye is displaced slightly by pressure upon it with the finger tip, or as a result of involuntary contraction of the eye muscles. These apparent movements are attributed to the successive stimulation of groups of receptors as the images move over the retina. When the eyes are moved voluntarily from one object to another in the visual field, images must sweep over the retina in a similar fashion, yet there is no apparent movement of stationary objects.¹⁰ Conversely, the movement of an object is perceived when it is followed by the eyes, though the position of its retinal image does not alter. It is quite evident that the perception of movement is very complex and cannot be explained in all its

aspects upon physiological grounds. It is suggested that the absence of an apparent movement of stationary objects when the eyes are turned from one part of the visual field to another is to be explained upon the basis of *attention*. The attention exercised by the observer in changing the fixation of his eyes from the one to the other point compensates, it is believed, for the movements of the images over the retina. In other words, the successive stimulation of visual receptors is ignored because the point to which the eyes are to be turned engages the attention at the moment that the eye movement takes place, or even before. The perception of the movement of an object pursued by the eyes must also depend upon cerebral processes.

Apparent movement is also produced by the stimulation of closely approximated retinal areas in rapid succession by a series of images of a stationary object. The two main factors determining this so-called *stroboscopic illusion* of movement are the time interval between the stimuli and the *angular separation* of the successive retinal images. A visual sensation of smooth motion is produced when the angular separation is about 1 degree or less and the intervals between the stimuli about $\frac{1}{10}$ second. At intervals of $\frac{1}{30}$ second or less no sensation of movement is produced. The illusion of motion is also lost if the time intervals are lengthened to $\frac{1}{2}$ second or greater, the impressions then becoming discreet.

Irradiation. Owing to chromatic and spherical aberration the images on the retina are not formed of geometrical points of light, but rather of bright points surrounded by diffusion circles. For this reason, and also probably as a result of the spread of the effect of the stimulus (*irradiation*) to neighboring neural elements of the retina, or even within the visual area in the brain, a bright area on a dark ground appears larger than a dark one of the same size upon a bright ground. In either instance the bright area encroaches upon the black area (see fig. 411).

¹⁰ An allied phenomenon and one which offers a similar problem to be solved is seen in cutaneous sensation. We are able, for example, to distinguish between the movement of the finger over a stationary object and the movement of an object over a motionless finger. In both instances receptors are stimulated successively.

CHAPTER LXXV

THE NATURE OF RETINAL PROCESSES; OBJECTIVE RETINAL PHENOMENA; COLOR VISION

THE NATURE OF THE RETINAL PROCESSES

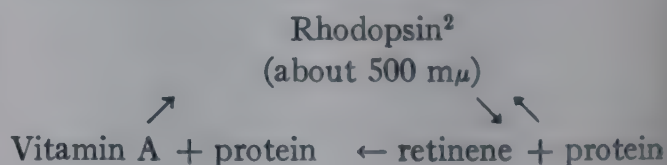
The photochemical mechanism of vision. Visual purple or rhodopsin is a rose-red photosensitive pigment found in the outer segments of the rods; it has not been demonstrated in the fovea. The pigment was discovered by Boll in 1876 and extracted from the retina by Kuehne in 1878. Its presence is essential for normal vision in dim light, and to it the nervous layer of the fresh retina, detached in the dark from the pigment layer, owes its reddish color (p. 956). It can be extracted from the retina by bile or a solution of bile salts, but the most effective extracting agent is digitonin. Visual purple either *in situ* or in solution is bleached by white light or by light of any wave length between 385 m μ and 650 m μ . Maximal bleaching is caused by green light with a wave length of about 502 m μ . In the living animal, and also to some extent in solution, the pigment regenerates in darkness. Chase's experiments suggest that another photosensitive substance in association with visual purple is necessary for regeneration. This associated pigment is particularly sensitive to blue light. The regeneration process is not affected by section of the optic nerve, but the drug santonin retards it, and in large doses causes yellow vision and night blindness. When one eye is illuminated, the other being shaded, bleaching of rhodopsin occurs only in the former.

If the eye of a rabbit is excised in darkness or in red light (light of a wave length greater than 650 m μ does not bleach the visual purple) and then exposed to an object clearly defined in light and shade, e.g., a window sash against the sky, an image of the object will be found to have been impressed upon the retina when it is examined in the dark room. The image is caused by the bleaching of the visual purple where the bright parts of the image fell upon the rods. The retina thus behaves like a photographic film; the image so obtained is called an *optogram* (see fig. 412).

Our knowledge of the chemistry of rhodopsin has been greatly advanced within recent years. It is a complex conjugated protein containing a carotenoid pigment as a prosthetic group. Its molecular weight has been variously estimated from 100,000 to 800,000. A value of 270,000 was ob-

tained by Hecht and Pickels. In solution or in the retina visual purple is bleached by intense light, first turning orange in color which changes rapidly to yellow and finally becoming 'colorless'. According to Wald, rhodopsin breaks down during bleaching into protein and an orange-yellow carotenoid pigment which he calls *retinene*.¹ Retinene is extractable by chloroform in which it shows a broad absorption band maximal at 387 m μ . In antimony chloride it shows maximal absorption at 664 m μ . The final colorless product is vitamin A. An extract of completely bleached retinas, therefore contains no rhodopsin but is rich in the vitamin. Under physiological conditions, vitamin A does not accumulate in the retina but is carried away in the circulation. Regeneration of rhodopsin from vitamin A occurs in the retina of the living animal during dark adaptation.

The rhodopsin vitamin A cycle is shown in the following scheme, modified from Wald.



¹ Lythgoe has given the name *transient orange* to the first product of the bleaching process and *indicator yellow* to the second derivative. This latter, as its name implies, behaves like an acid-base indicator, being chrome yellow between pH 3.3 and 4.0, a deep lemon yellow at neutrality and a pale lemon between pH 9.3 and 10.0. Indicator yellow is also formed immediately from rhodopsin by heat and by the action of acids and alkalis. The mixture of yellow pigments formed during bleaching was called "visual yellow" by Kuhne.

² The photosensitive pigment in the retinas of fresh water fish differs from that found in the retinas of most vertebrates including the marine fishes. This pigment, which is truly purple in color, has been named *porphyropsin* by Wald. It follows a retinal cycle identical with that of rhodopsin except that vitamin A₂ takes the place of vitamin A(A₁), and the retinene produced during bleaching has, in chloroform, an absorption band with a maximum at 405 m μ instead of at 387 m μ . Wald has made the highly interesting observation that the type of pigment present in the retinas of the euryhaline fishes (those species which migrate from salt to fresh water or vice versa) is determined largely by the waters, salt or fresh, in which they are spawned. Thus, in fish, such as salmon, which spawn in fresh water (anadromous forms) the predominant pigment is porphyropsin, whereas, in those, such as, the fresh water eel which spawn in the sea (catadromous forms) rhodopsin predominates.

(328 $m\mu$ in chloroform)	(387 $m\mu$ in chloroform)
(615 $m\mu$ in antimony chloride)	(664 $m\mu$ in antimony chloride)

In the completely bleached isolated retina or in the intact eyes of animals fed upon a diet deficient in vitamin A, regeneration of rhodopsin cannot take place, though in the former some regeneration from retinene may occur in darkness. It will be recalled that vitamin A deficiency is one cause of night blindness (hemeralopia).

Convincing evidence can be cited for the view that the first phase in the retinal process whereby radiant energy is converted to nerve impulses (electrical energy) is photochemical in nature.



FIG. 412. Optogram of a window in a rabbit's eye. The white rectangular area is a layer of colorless medullated nerve fibers and the circle at its center is the optic disc. (From Howell after Kuhne.)

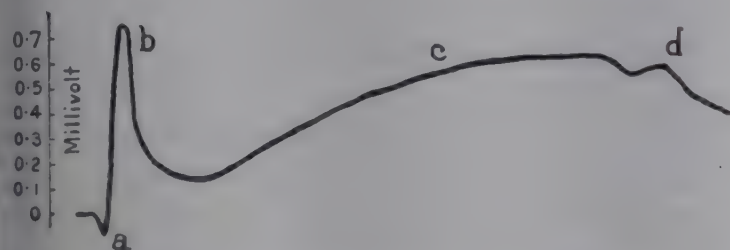


FIG. 413. Electroretinogram. (From Granit, re-drawn.)

There can be little doubt that rod vision is dependent upon such a process and that the photochemical pigment, rhodopsin plays an essential rôle in twilight vision. When the absorption spectrum of this pigment is plotted (reciprocals of the minimum energy required for bleaching along the ordinates, and the wave lengths along the abscissae) the graph is found to be identical in shape with the visibility curve for twilight vision (fig. 416). A curve formed by plotting the rate of bleaching of visual purple against the wave length coincides almost exactly with the absorption curve; in other words, visual purple follows Draper's law which states that chemical change is produced in a photosensitive material only by those waves which are absorbed. The significance of these facts is unmistakable.

Though the visibility of the dark adapted eye and the absorption curve of visual purple are identical in *shape*, there is a difference of 7 $m\mu$ in the maxima of the two curves, the maximum of the former lying at 510 $m\mu$ (Hecht and Williams), that of the latter at about 503 $m\mu$. An explanation for this discrepancy will be offered presently. The retina also obeys the Bunsen-Roscoe law formulated for photochemical processes in general, namely, that for the production of a given photochemical effect a constant quantity of energy is required which can be distributed within certain limits by varying either the illumination or its duration. In other words, the product of the

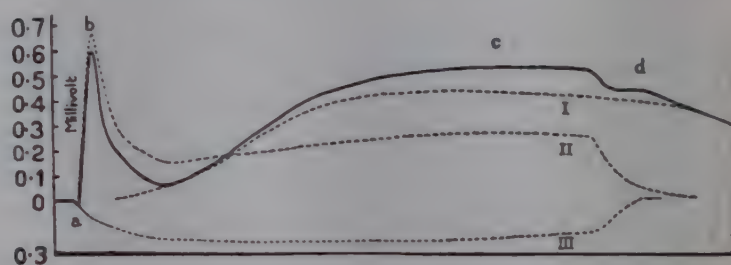


FIG. 414. Analysis of composite retinal electrical response (cat's eye) at two intensities, 14 ml. and 0.14 ml. and area of 1661 sq. mm., viewed at a distance of 70 mm. Components, broken lines. Composite curve drawn in full. The *a*-wave is broadened slightly out of scale to show its derivation more clearly. (Granit, *J. Physiol.*, Vol. LXXVII, 1933.)

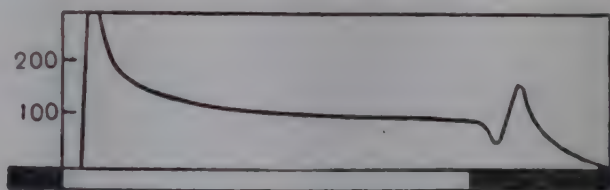


FIG. 415. Curve of frequencies of impulses in optic nerve. (After Adrian and Matthews.)

illumination (*I*) and the time of exposure (*T*) is constant, $\text{Energy} = kIT$.

The difference between the maxima of the absorption curve of visual purple and the twilight visibility curve is actually somewhat less than that given above. Dartnall and Goodeve point out that the visibility curves should be plotted using an equal quantum spectrum (the quantum of light energy varies with the wave length) and not an equal energy spectrum (p. 958). When this is done the maximum of the twilight visibility curve is at 506 $m\mu$ or 507 $m\mu$. A difference therefore of only 4 or 5 $m\mu$ exists between the maxima of the two curves. In the recent experiments of Lythgoe with purified preparations of visual purple maximum absorption was obtained at 502 $m\mu$. Hecht and Williams have pointed out that a discrepancy of even 7 $m\mu$ may well be accounted for

by the fact that the absorption curves of rhodopsin have been determined of necessity upon *solutions* of the pigment and some difference should be expected between curves so obtained and the absorption of visual purple as it exists in the retina.

Important evidence for the photochemical nature of the initial stages of the visual process has been obtained by Hecht through the study of a much simpler photochemical mechanism, namely, that afforded by certain invertebrate forms. The body surface of a clam, *Mya*, of an ascidian, *Ciona*, and of a mollusc, *Pholus*, possesses light sensitive areas. When exposed to light the syphons of *Mya* after a long latent period become retracted. Several points of similarity between this reaction, which is undoubtedly photochemical in nature,

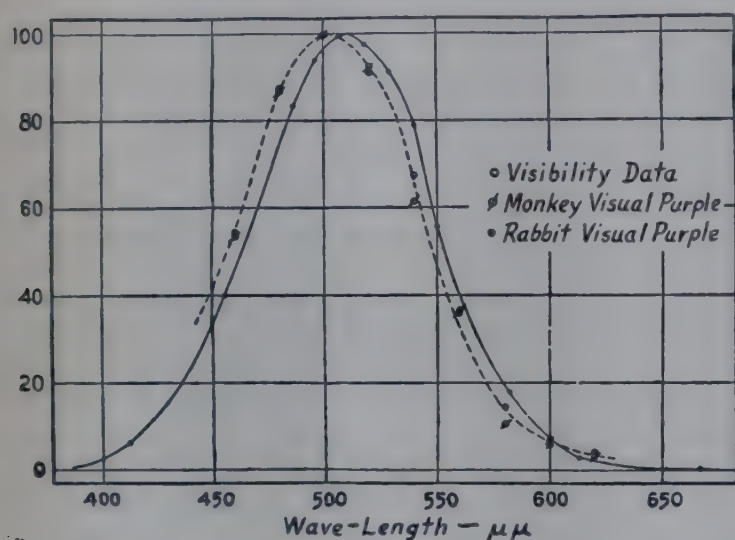


FIG. 416. Relation between absorption spectrum of visual purple in bile salts solution (monkey and rabbit) and absorption spectrum of sensitive substance in the rods as given by the visibility curve of figure 400. Though the two curves are identical in form, the visibility curve is shifted 7 or 8 $\mu\mu$ toward the red. (After Hecht.)

and vision have been demonstrated. *Mya* shows light and dark adaptation, its sensitivity being increased in the dark and reduced by a stay in daylight. The reaction follows the Bunsen-Roscoe law; and the Weber-Fechner law is obeyed over a limited range of moderate light intensities, the ratio $\frac{\Delta I}{I}$, as in the case of the retina, increasing at high and at low intensities. The reaction also shows selective spectral sensitivity, the energy required to elicit a response varying with the wave length.

The photochemical theory, though satisfactory for rod vision, failed to explain daylight vision, for no photosensitive pigment had been demonstrated in the cones of the mammalian retina. Nevertheless, as a result of his studies, Hecht had thought it highly probable that foveal vision was also dependent upon a photochemical mechanism. The visibility curve of the light adapted eye is

identical in *shape* with that for twilight vision and consequently with the spectral absorption curve of a solution of visual purple. But the *maxima* of the three curves do not coincide; that of the light adapted eye being at 550 $m\mu$. The identical shapes of the curves, nevertheless, suggest very strongly that cone vision is also dependent upon a photochemical substance—possibly visual purple in high dilution. A low concentration of the pigment in or around the cones would account for its not being evident; yet its function would not necessarily be abolished thereby, for it has been shown that certain photochemical substances, e.g., silver nitrate and cyanin, do not lose their properties when spread in very thin films. However, the difference between the maximum of the daylight visibility curve and that of the absorption curve (about 45 $m\mu$) were considered too great to be accounted for purely upon the basis of changes in the properties of the pigment during its extraction.

The results of Wald's researches have largely resolved the difficulty of extending the photochemical theory to cone vision. He extracted the dark-adapted retinas of chickens which contain chiefly cones. Such an extract would contain rhodopsin derived from the small rod population mixed with cone pigment if such existed. Upon exposing the extract to red light, to which the rods are only slightly sensitive, bleaching occurred, absorption being maximal at 575 $m\mu$. Subsequent exposure of the extract to white light caused bleaching characteristic of rhodopsin with maximal absorption around 508 $m\mu$. The initial bleaching by red light was due, presumably, to a photosensitive pigment derived from the cones. The spectral properties of this pigment indicate that it is violet in color. Wald has therefor named it *iodopsin*. A comparable pigment has been obtained by Chase from the retinas of frogs. The maximal sensitivity of chicken cones is at 580 $m\mu$. and that of the rods at about 520 $m\mu$. The former figure is in close agreement with the maximal absorption (575 $m\mu$.) of iodopsin.

The following expression has been used by Hecht to illustrate the photochemical reaction:

light

$S \xrightarrow{\text{light}} P + A$, where S is the photosensitive substance which breaks down into P and A in the light; these in turn are built up into S in the dark. The two opposing reactions proceed simultaneously, the velocity in either direction depending upon the intensity of the light and upon the concentrations of S and of P + A. Provided that there is a sufficient supply of S, a certain

dark

quantity of absorbed light energy causes a constant quantity to be decomposed. When the dark adapted eye, in which visual purple (S) is in high concentration, is exposed to light the reaction proceeds rapidly to the right until equilibrium is established, light adaptation is then complete. From then on, synthesis and decomposition proceed at equal rates and the concentrations of S, P and A are maintained at constant levels, so long as the light intensity does not alter. In darkness the reaction proceeds to the left, rapidly at first but then more slowly as the equilibrium point is approached. At full dark adaptation equilibrium is again established.

The decomposition products of the primary photochemical reaction $S \rightarrow P + A$ are supposed to catalyze a secondary chemical reaction whose products are immediately responsible for stimulating the afferent nerve terminals

NERVOUS MECHANISMS. The photochemical mechanism constitutes the means whereby light energy, through the breakdown of rhodopsin, causes a visual stimulus to be produced. But this is merely a preliminary phase in the retinal process which is essentially nervous in nature. It must always be borne in mind that the retina is an outgrowth of the brain. Functionally it is a "true nervous center" (Cajal). Unlike any other sense organ its receptors are in close association with synaptic connections, and many of the phenomena of the retina are expressions of interaction between neurons. For example, phenomena which have already been described for nervous centers, e.g., spatial and temporal induction, inhibition, rebound, etc., have been demonstrated for the retina. Adrian and Matthews demonstrated spatial summation, using the shortening of the latency of the optic nerve discharge as the criterion of increase in the retinal response. They found that as compared with the illumination of a single area simultaneous stimulation of four separate retinal areas caused a marked shortening of the latent period. Granit and Davis have shown by means of the electroretinogram the occurrence of temporal summation in the human retina. They found that when the retina is stimulated by two subliminal stimuli separated by an interval of about 50 m.sec. summation to the threshold results. The effect of the first stimulus persists, though gradually declining, for 135 m.sec.; after this interval, a second stimulus produces no response unless it is of threshold value itself. The retina, then, must not be looked upon simply as a mosaic of separate points each connected to the nervous system by its own nerve fiber and acting independently of the rest (Adrian and Matthews).

OBJECTIVE RETINAL EFFECTS CAUSED BY LIGHT STIMULI

Illumination of the eye causes (a) bleaching of the visual purple, (b) alteration in reaction of the retina from alkaline to acid, (c) histological changes in the pigment cells and cones of certain cold-blooded species, and (d) changes in electrical potential.

Little is known of the chemistry underlying the production of acid in the stimulated retina, but the acid is probably lactic derived from the breakdown of glucose, for it has been shown that the retina as compared with other tissues has a strong glycolytic action. The acidity increases with the intensity of the stimulus and is greatest with yellow-green light.

Histological changes in the retinas of frogs, fish and certain other cold-blooded forms occur upon stimulation, but have not been demonstrated in mammals. They consist of movements of the pigment granules of the cells of the outer retinal layer (p. 956) and retraction of the bases of the cones from the pigment cells, leaving an interval between the two. The contraction of the cones is apparently a reflex phenomenon, for it occurs upon stimulation of the opposite eye or even, according to some, upon exposure of the skin to light. Swelling of the rods in bright light, and then shrinkage in the dark so that they become separated by a distance of from 0.5μ to 0.8μ are other retinal phenomena seen in these species.

RETINAL ACTION CURRENTS; THE ELECTRO-RETINOGRAM. When the cornea and the optic nerve or the posterior pole of the darkened eyeball are connected through a galvanometer, a current is set up (*demarcation current*) with the cornea as the positive pole. A steady deflection of the galvanometer results. The cause of this current is not clearly understood. When a light is thrown into the eye a series of potential changes is produced which can be recorded as a corresponding sequence of waves. These are the retinal action currents, the record is called an *electroretinogram*.

Holmgren, the Swedish physiologist, was the first (in 1866) to demonstrate retinal action currents when the eye is stimulated by a beam of light. From then to the beginning of the present century they were studied by a number of investigators, including Dewar and McKendrick, Waller and Gotch. They were recorded with the string galvanometer by Einthoven and Jolly in 1908 and by Piper, by means of the capillary electrometer, in a series of studies from 1908 to 1911. In recent years with the development of more delicate methods of recording the subject has been reinvestigated by Chaffee, Bovie and Hampson, by Hartline and by Granit and his associates.

In the earlier experiments records were obtained from the surviving excised eye, and in many instances after removal of the anterior half of the globe, or from preparations in which dissection had caused a considerable degree of trauma. Though it was necessary to place one electrode directly upon the retina in order to prove the retinal origin of the currents,³ better results can be obtained by leaving the eye in situ and placing one electrode upon the cornea of the illuminated eye and the other (indifferent electrode) upon the eye of the opposite side or upon any moist surface of the body. Typical electroretinograms are obtained in this way. Hartline has applied this method to the human subject by means of water-tight goggles fitted to the eyes and filled with a 0.9% saline. The goggle in front of the eye to be illuminated holds the differentiated electrode and is fitted with a convex lens to correct for the optical effect of the solution. The indifferent electrode is fitted into the other goggle. In another method employed by Hartline for man, a cotton-tipped electrode is applied directly to the illuminated eye after anesthetization with a 2% solution of holocaine; the indifferent electrode is placed in the mouth.

The most satisfactory preparation from which to record the electroretinogram is the decerebrate animal, since perfect immobilization is thus secured, as well as full pupillary dilatation. The indifferent electrode is placed upon brain tissue on the proximal side of the decerebration cut, and the other electrode on the cornea. The recording instrument most commonly employed is the string galvanometer or some type of oscillograph, the currents being first conducted through a valve amplifier.

Analysis of the record. The electroretinogram (see fig. 413) consists of four waves, designated *a*, *b*, *c* and *d*. The *a* wave is a small, rapid negative deflection—a sharp notch below the base line—which appears after a short but variable latent period. The wave *b* is a well-marked positive deflection of about 8 millivolts, and *c* is a slow, prolonged positive wave which declines gradually though the eye remains constantly illuminated. The *d* deflection is a small positive change which appears after a brief latency when the light is cut off; for this reason it is usually referred to as the “off effect.”

Einthoven and Jolly concluded from an analysis of their records that the “on effect” (*a*, *b*, and *c* waves) was a composite deflection due to the algebraic summing of the potential changes of three separate retinal processes. The recent researches of Granit and his associates have confirmed and extended the work of these earlier investigators. The three processes have been designated *P*, *P_{II}* and *P_{III}*, since they can be

³ A characteristic record is not obtained after removal of the nervous layers of the retina.

made to disappear in this order by corresponding degrees of anesthesia. *P_I* is responsible for the sustained potential of the *c* deflection; it is abolished by light anesthesia, leaving the fast initial waves (*a* and *b*) unchanged. With deeper anesthesia the *b* wave becomes smaller and then disappears, leaving the component responsible for the *a* deflection. This is a prolonged negative deflection (see fig. 414).

In the final stage of anesthesia the negative component disappears and the retina, having apparently suffered an irreversible change, cannot be made to respond again. The *P_I* component is only seen at high light intensities and in the dark adapted eye; *P_{III}* is also absent, as a rule, at low levels of illumination. *P_{II}* is abolished by asphyxia. Thus, by varying the illumination, by anesthesia or asphyxia, records can be obtained composed of *P_{II}* + *P_{III}*, of *P_I* + *P_{III}*, of *P_{II}* alone or of *P_{III}* alone.

The three processes responsible for the electrical changes in the retina arise in the nervous layers and the potential changes do not represent nerve fiber responses since they cannot be obtained by placing the differentiated electrode upon the optic nerve entrance; *synaptic connections are essential for their production*. The *b* wave, for example, increases in amplitude with the illumination intensity; whereas, as will be seen presently, the magnitude of the action potentials of the optic nerve does not vary with the strength of the stimulus. Furthermore, the latency of the retinal response diminishes as the intensity of the light or the size of the illuminated area on the retina increases—additional evidence of synaptic transmission.

P_{III} (component responsible for *a* wave) is, according to Granit, an inhibitory process. *P_{II}* (responsible for *b* wave) is excitatory in nature and is followed by a discharge of impulses in the optic nerve. *P_I* (component causing *c* elevation) is not associated with a discharge of impulses in the optic nerve. The “off effect” (*d* wave) is considered to be a rebound phenomenon (p. 813) resulting from the cessation of the inhibitory process *P_{III}* and the release with consequent enhancement of the slower processes *P_I* and *P_{II}*, particularly of the latter.

ACTION POTENTIALS IN THE OPTIC NERVE. The action currents in the optic nerve of the conger eel were investigated by Adrian and Matthews. The optic nerve of this species is unusually long and contains relatively few fibers—facts of considerable technical advantage. The potentials were recorded by a capillary electrometer after passage through a four valve amplifier.

The nerve is almost “quiet” in the dark but a light flashed into the eye causes a discharge of impulses. If the nerve is crushed between the eye and the recording electrodes no potential waves appear. The total response to a flash lasts for about 15σ. Depending upon the intensity and

area of illumination, the latent period varies from 0.1 to 0.5 sec., becoming shorter with increasing strength of stimulus. The frequency of the impulses show two maxima, one (300 per sec.) associated with the "on effect" of the electroretinogram, the other with the "off effect" (see fig. 415).

The amplitude of the impulses (action potentials) or their grouping does not vary with the intensity of the stimulus or with the area of the retina illuminated (p. 786). On the other hand, an increase in either of these factors increases the impulse frequency and shortens the latency of the nerve response. Hartline has recorded the responses of a single optic nerve fiber and also finds that a change in frequency of the impulses, but not in their amplitude, results from varying the intensity of the stimulus. The effect of varying the area is limited to images under 1 mm. in diameter, the greatest effect being observed with variations in the size of images of 0.3 mm. in diameter or less. Though, as just stated, the latent period (i.e., the time elapsing from the application of the stimulus to the appearance of the first impulse in the nerve) is variable, the retinal nerve time (i.e., the interval between the *a* deflection of the electroretinogram and the commencement of the impulse discharge in the nerve) is constant with varying strength of stimulus. Variations in latency of the nerve response are therefore due simply to corresponding variations in the latent period of the retina.

As mentioned above, Granit's analysis of the retinal response shows that process II alone is responsible for the initiation of a discharge in the nerve. The impulses therefore reach their maxima where this process causes the *b* deflection and at the "off effect" (*d*) where rebound occurs as a result of the cessation of the inhibitory process (PIII).

The burst of impulses at the "off effect" is of special interest; such is not seen in the nerve fiber of any other receptor organ. Its significance, however, seems clear. The signalling of darkness to the centers in the brain is of just as great importance in the life of the animal as the signalling of light. A shadow or a dark object in the field of vision may indicate food or the approach of an enemy.

The decline in frequency of the impulses, i.e., between the two maxima, though the stimulus persists is difficult to explain. It might be attributed to sensory adaptation (p. 806). Yet how can such an explanation be reconciled with our own sensations, for, as a rule, an object at constant intensity of illumination does not appear less bright while we continue to look at it. On the other hand, it is certainly true that a moving image, which stimulates groups of retinal elements successively, is seen more easily and is more likely to attract

attention than a stationary one. Indeed in many species an immobile object apparently is not perceived. Is it that in the *intact* and *conscious* animal, a sustained sensation of brightness of a stationary object under constant illumination is due to the incessant involuntary eye movements which, by causing successive stimulation of groups of retinal elements, nullify the effect of adaptation and that the optic nerve transmits a continuous stream of impulses at high frequency?

COLOR VISION

Color perception is a function of the light adapted eye (p. 968); being entirely dependent upon the cones. Animals whose retinas contain only rods are therefore completely color blind. When the illumination of the field of vision is gradually reduced, red objects first lose their color, then those colored yellow, green or blue, in this order, become colorless. In dim light the surroundings are almost without color, being seen in shades of gray, black and a bluish white. The blue color of deep twilight is believed to be a peculiar function of the rods. Color possesses three qualities or attributes—hue, brightness and saturation.

Hue or *tone* is dependent entirely upon the wave length of the rays. Thus, red, yellow, green, blue and violet are different hues.

Brightness (*brilliance* or *luminosity*) is determined by the intensity of the rays,⁴ whatever their wave length, falling upon the retina. Thus, there can be many degrees of brightness within a single hue. Of two objects having the same hue and illuminated to the same degree, the one which absorbs the smaller proportions of the rays of the specific wave length and reflects the greater proportion appears the brighter. The different brightnesses of a given hue may be compared to a number of mixtures of black and white made up in various proportions to produce a graded series of shades of gray. For example, just as any shade of gray may be produced by adding black to white, so a paint of a given hue can be reduced to any degree of brightness by mixing with it a suitable quantity of black. It is very difficult for one to match the brightness of two different colors (heterochromatic photometry). The method mentioned in footnote p. 966 is resorted to, which overcomes the natural tendency to confuse brightness with hue and saturation.

Saturation (or *purity*). As in the case of brightness, color saturation may show infinite variations in degree within a given hue. Red is a more saturated color than

⁴ It might be more strictly correct to say "intensity of sensation" rather than "intensity of the rays" for we have seen that dark adaptation causes a shift in the point of maximal luminosity, but as measured physically of course no shift occurs.

pink. The difference is due to the relative quantities of white light with which the red light is mixed. For example, the saturation of a paint of a given hue can be reduced by mixing white with it. The mixture reflects white light as well as light of the wave length by which its hue is perceived. The saturation of a colored light could be readily determined by means of the spectroscope. Thus, a fully saturated red or green (homogeneous or monochromatic) light would give a red or a green color at the corresponding part of the spectrum, whereas, if either color contained an admixture of white light, all the spectral colors would appear, their intensity depending upon the quantity of white in the mixture.

THEORIES OF COLOR VISION

None of the many theories of color vision is capable of accounting for all the observed phenomena, either of normal vision or of color blindness. The theory suggested by Young (1807) and supported with extensions and elaborations by Helmholtz (1853) is the best known, the simplest and perhaps open to the fewest objections.

THE YOUNG-HELMHOLTZ THEORY. Though scarcely necessary it may perhaps be an advantage to recall some elementary principles. White light is a combination of light rays of wave lengths from about $720\text{ m}\mu$ to $350\text{ m}\mu$, and can be split into its constituent colors—red, orange, green, blue and violet—by means of a glass prism. These spectral colors can be recombined again to produce white light of the *same intensity* as the original light from which they were derived (Abney's law). It is not necessary, however, for one to use all these colors in order to produce white; only three, namely, red, green and blue (or violet) combined in suitable proportions, are required to produce white or any other color we may desire. Red, green and blue (or violet) are therefore called the *primary colors*. But pure spectral lights, not pigments, (see footnote p. 981) must be employed in the combinations. If we should set up three lanterns, of which one emitted red light, another green and a third blue (or violet), then by throwing one upon a screen or a blend of two or of all three, we could produce any color of light we chose as well as white. Red and green would give rise to yellow, red and blue or violet to purple, and so on; all three colors, mixed in equal proportions, would produce white. These are uncontested facts to which any theory of color vision must conform.

The Young-Helmholtz theory claims that there are three types of percipient elements in the retina, each containing a substance which is acted upon by one or other of the primary colors. The sensa-

tion of white and of the many different colors is due to the stimulation of the three elements at different relative intensities (see fig. 417). Pure red light for example, stimulates strongly those cones containing the "red substance" and the other types very feebly; green, blue or violet lights stimulate powerfully those containing the green, blue or violet substances, respectively; the sensation of white results when all three types are stimulated equally.

It is evident that this theory is in accord with the established facts in respect to color mixing. It also gives a plausible explanation of the common types of color blindness on the assumption that one or other type of cone is defective or lacking. For example, failure to appreciate red would be due to deficiency of the red-sensitive substance, absence of sensitivity to

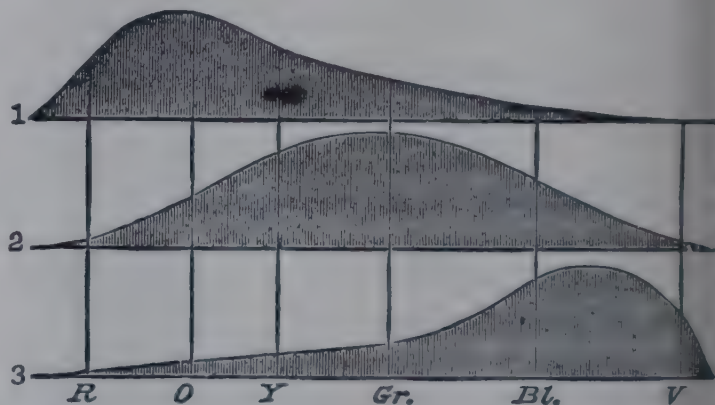


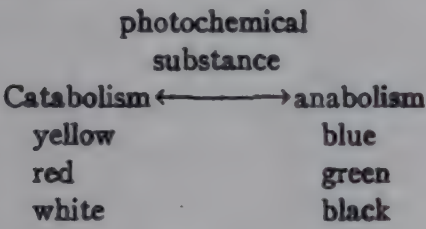
FIG. 417. Diagram of three primary color sensations. 1 is the so-called 'red,' 2 'green,' and 3 'violet' primary color sensation. R, O, Y, etc., represent the red, orange, yellow, etc., colors of the spectrum. The diagram illustrates, by the height of the curve in each case, how the several primary color sensations are respectively excited to different extents by vibrations of different wave-lengths. (After Helmholtz.)

green to lack of the green substance. Temporary partial color blindness can be produced by intense stimulation of the retina by one of other of the primary colors, which is readily explained upon the basis of fatigue of the corresponding type of sensitive element. For example, if one looks at the sun for a couple of minutes through a red glass and then directs the eyes to differently colored objects, the perception of red is found to be lost—red geraniums appear black, yellow flowers green and pink roses sky blue (rose color being a blend of pink and blue). The eye fatigued in a similar way by green light sees the foliage colored bluish or reddish gray.

The theory fails, however, to explain the absence of color sense in the most peripheral part of the retina (p. 968). For if the sensation of white is due to the equal stimulation of three types of retinal receptor (which, according to the theory, must therefore be present in this part of the retina), why does not a sensation of color result when the

different types are stimulated unequally, as by red, green or blue? For the same reason the theory fails to explain complete color blindness (p. 980); nor does it fit the duplicity theory, or account satisfactorily for positive after images (p. 982). An objection which will be mentioned presently (but which really seems beside the point) is in respect to the claim that yellow is as much as a unitary sensation as either of the three so-called primary color senses.

Hering's theory (theory of opponent color pairs). This theory postulates the existence of three substances in the retina which give rise to three pairs of elementary and antagonistic sensations, namely, those of *yellow* and *blue*, *red* and *green*, and *black* and *white*. One sensation of each pair—*yellow*, *red* or *white*—is due supposedly to the breakdown—*catabolism* or *dissimilation*—of a corresponding hypothetical color-sensitive substance. The other member of the pair—*blue*, *green* or *black*—results from synthesis of the respective substance—*anabolism* or *assimilation*—Thus:



The theory offers a plausible explanation of successive contrast and negative after images (p. 982). A red or yellow light, for example, causes a green or a blue after image, respectively. The red (or yellow) image causes presumably, through catabolism, the reduction of the red-green (or yellow-blue) substance, which upon withdrawal of the light will undergo more rapid synthesis and, as a consequence, the opposite sensation of green (or blue). The theory fails however to explain satisfactorily positive after images. There is a certain psychological basis for grouping the six sensations into antagonistic pairs, as was emphasized by Hering, and by Goethe before him. It is pointed out that yellow, red and white are warm, bright and cheerful; blue, green and black are cold, dull and sombre.⁶

It will be noticed that this is a tetrachromatic theory, yellow being assumed to be a primary sensation like red, blue and green, and not, as in the Young-Helmholtz theory one compounded of red and green. Justification for this supposition is drawn from psychological considerations. Pure yellow, it is pointed out, is a sensation just as unitary as any one of the other three colors, for like them, no other color appears to be blended in it. We can see the yellow in yellow-green,

for example, the red and blue in purple whereas pure yellow like pure red, green or blue is a single unalloyed sensation. Nevertheless, a mixture of red and green *does* give yellow, a fact explained by the Young-Helmholtz theory. The antagonism of the single members of any of the color pairs postulated by this theory is emphasized by the fact that singles of any pair do not mix to give a composite color; e.g., a yellow-blue or a red-green sensation is unknown, whereas, the singles of *different* pairs combine to give various shades, e.g., orange, green-blue, yellow-green and purple. Of course, it is impossible to see, in terms of the theory, how a yellow-blue or a red-green sensation could be produced. It would mean that either of these sensations was caused by the simultaneous breakdown and synthesis of the same substance. But when we consider a sensation of gray this is precisely the conclusion to which the theory leads us. The theory also fails to account for the two well-known forms of color blindness (protanopia and deuteranopia, p. 979) and for McDougal's observation that red light seen by one eye and green light simultaneously by the other give a sensation of yellow. Fusion of the two sensations must be a cerebral process; in order therefore to explain the sensation of yellow there is no need to postulate the breakdown of a photochemical substance in the retina.⁶ As already mentioned, the Young-Helmholtz theory is supported by experiments in color matching, whereas Hering's theory is not.

The Ladd-Franklin theory attempts to overcome the objections that have been raised to the two foregoing theories and combines some of the features of both. It has been developed upon an evolutionary basis. Like Hering's it maintains the unitary nature of the sensation of yellow and is therefore a tetrachromatic theory; it is in agreement with the Young-Helmholtz view in that it postulates an initial tri-receptor photochemical mechanism, namely, the production of three elementary excitant substances by the action of red, green and blue light, respectively. It also conforms with the duplicity theory.

The colorless sensations—white, black and gray—are presumed to result from the action of light upon a substance (white substance) present in the rods (see fig. 418); it is the most elementary of the photochemical substances. Retinas possessing only rods and the most peripheral portions of the retina of man are therefore devoid of color sense. The cones are believed to be evolved from rods (Cajal) and accompanying this development the primitive white sensitive substance, through an intermolecular rearrangement, becomes responsive not only to white but to yellow (Y substance) or blue (B substance) light as well, yielding in each case

⁶ Goethe remarks, "We find from experience that yellow excites a warm and agreeable impression. . . . This impression of warmth may be experienced in a very lively manner if we look at a landscape through a yellow glass, especially on a grey winter's day."

⁶ An experiment of Abney is readily explained by the Young-Helmholtz hypothesis but not by Hering's. If one eye is fatigued by red (red elements being thus rendered relatively unresponsive) and then directed to a patch of pure yellow the latter appears greenish yellow.

a reaction product which sets up the nerve impulse. Visual evolution has reached such a stage in the retina of the honey bee, it being sensitive to white, yellow and blue light but not to red and green. This type of vision is also characteristic of the midzone of the human retina. The final change occurs in the yellow sensitive substance; acted upon by red or green light it gives rise to reaction products upon which the corresponding sensations depend. When the yellow and blue excitant substances are produced simultaneously they recombine to form the original substance from which they have been derived, and so to give rise to the sensation of white. Thus a blend of yellow-blue is impossible. Similarly the red and green substances if produced simultaneously combine to produce the sensation of yellow; if simultaneous production of the blue excitant occurs as well, the sensation of white results.

Though the theory has certain very attractive features, others of its postulates cannot be reconciled with observation. The most serious defect—a defect common to it and the theory of Hering—is its contradiction of Mueller's law (of specific nerve energies, p. 808).

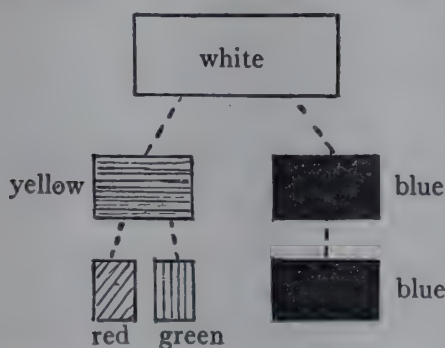


FIG. 418. Illustrating Ladd-Franklin theory.

The theory seems to imply that the white substance gives rise, according to the type of stimulus, to any one of the four excitant substances within the compass of a single cone, which runs counter to the modern conception that the nerve fiber can carry only one type of message, i.e., that the character of the nerve impulse in whatever fiber it is transmitted is essentially the same.

Roaf's theory. This is a modification of the Young-Helmholtz trichromatic theory. Roaf concludes from the results of his determinations of the thresholds for color discrimination that there are three sets of color receptors: (a) those sensitive to long waves—from the red end of the spectrum to about $590\text{ m}\mu$, (b) those sensitive to medium and long waves, a spectral region extending from the red end to about $500\text{ m}\mu$ and (c) those sensitive to the whole of the visible spectrum. Red light stimulates all three sets; green stimulates *b* and *c*; blue stimulates only *c*. The sensation of white is due to the unequal stimulation of all three types of receptors in the order, $a < b < c$. It is suggested that the cones are the *a* and *b* receptors, and the rods the *c* receptors; the latter are the only ones stimulated by the short wave lengths and would therefore be those giving rise to a blue or violet sensation. This would account for the blue color of twilight vision—the so-called "blue sensa-

tion of the rods" of other observers, and for the blue appearance of a light of any wave length when it falls on the peripheral retina; it would also explain the impairment in the perception of blue in conditions associated with defective rod function e.g., night blindness and retinitis pigmentosa. The suggestion is made that the behavior, of the three sets of receptors may be due to the presence of colored oil globules acting as filters. Colored globules are found in the retinas of amphibians, reptiles and birds. The inner segments of the cones of the domestic hen, for example, contain well defined oil droplets, reddish in some cones, yellow green or colorless in others. Wald has isolated three carotenoid pigments from chicken cones which are closely comparable in their colors with those of the oil globules. The first could serve to transmit red light the second yellow and green and the third, light of all wave lengths. Oil globules have not, however, been demonstrated in the mammalian retina but in those animals in which they are found it is not improbable that they serve as filters for the differentiation of color.

THE DISTRIBUTION OF THE COLOR SENSE. The determination of the extent of the retinal areas sensitive to the three primary colors is important in many conditions, for changes in the distribution of the color sense may be one of the first changes to be detected in certain visual defects. When the normal retina is mapped out by means of the perimeter (p. 1007) it is found that the three primary sensations are distributed over four areas of different sizes which are centered, roughly, at a point a little to the inner side of the fovea. The largest area is for the perception of blue, a short distance within its circumference is the boundary of a smaller area for yellow. Next in size is the area for red; the area sensitive to green is the smallest; this last area is therefore trichromatic (sensitive to all three primary colors). A band surrounding it, i.e., the interval between the boundaries of the red and green areas is sensitive to blue, yellow and red, the third zone to yellow and blue, and the fourth to blue alone. The retina lying beyond the blue area as far forward as the ora serrata is achromatic, being sensitive only to white light, a colored object appearing gray or black. Minor variations in the extent and shape of the color fields are seen in different persons. The margins of the fields are rather irregular and include more of the nasal than of the temporal part of the retina, i.e., more of the temporal part of the visual field (p. 1007).

The different color zones have not a common boundary around the optic disc (blind spot) but show a concentric distribution the reverse of that

just described for the periphery. When color perception is investigated up to the margins of the disc the boundary for green is reached first, that for red next, then that for yellow and finally that for blue. A narrow zone beyond the latter and immediately surrounding the disc is sensitive only to white light.

COLOR BLINDNESS

We have seen that normal color vision is trichromatic, i.e., white light or any color can be matched by a mixture of three primary colors in suitable proportions. Color blindness is usually classified upon this basis into *anomalous trichromatic*, *dichromatic* and *monochromatic* types. The three forms could be explained in terms of the Young-Helmholtz theory by presuming that one or other color sensitive substance—red, green or blue—was defective or absent.

ANOMALOUS TRICHROMATIC VISION. In this defect, which was discovered by Lord Rayleigh in 1882, there is not complete blindness for any color, but the appreciation of red or of green is less than normal. The anomaly with respect to red is called *green-sightedness*, *partial protanopia* or *protanomaly*.

Subnormal perception of green is called *red-sightedness*, *partial deuteranopia* or *deuteranomaly*. The subject of partial protanopia in order to match a homogeneous yellow light with a mixture of red (λ 671 m μ) and green (λ 536 m μ) requires the addition of far more red than does a person with normal vision; the partial deuteranope requires more green. This is called the Rayleigh test. Anomalous trichromatic vision is looked upon as a transition stage between normal vision and the dichromatic form of color blindness.

DICHROMATIC VISION. There are three types of dichromatic vision, *protanopia* or *red-blindness*, *deuteranopia* or *green-blindness*⁷ and *tritanopia* or *blue-blindness*. For the sake of illustration we may presume that in this form one of the three photosensitive substances postulated by the Young-Helmholtz theory is lacking. Color vision is therefore a function of two variables instead of three, i.e., only two colors, green and blue in protanopes, red and blue in deuteranopes, or red and green in tritanopes, are required to match white or any color of the spectrum.

⁷ Many authorities, especially adherents of the trimeric hypothesis of color vision, refer to either protanopia or deuteranopia as red-green or green-red blindness, since in both conditions red and green are confused. Similarly, tritanopia is called yellow-blue blindness.

Protanopia is the commonest form; tritanopia is very rare. To the protanope the red end of the spectrum is shortened; red objects appear dark and may be confused with dark green, dark gray, dark blue or black. There is no darkening of the red end of the spectrum in deuteranopia. In protanopia the red-yellow part of the spectrum appears as different shades of green. John Dalton (1798), the famous English chemist, suffered from this type of color blindness and was the first to give a scientific account of it (1794); hence the term Daltonism. He says "Crimson has a very *grave* appearance, being the reverse of every showy and splendid colour. Woolen yarn dyed crimson or dark blue is the same to me . . . the colour of a florid complexion appears to me that of a dull opaque blackish-blue upon a white ground."

It has just been stated that in dichromatic vision, white or any spectral color can be matched by the mixture of two colors in suitable proportions. It follows therefore that in deuteranopes, a certain region of the spectrum (between λ 505 m μ and λ 492 m μ) appears colorless. This *neutral region* is blue-green to the normal eye. Wave lengths within this range therefore give the impression of a dirty white and when combined with other rays have a corresponding value in the mixture.

When mixed with other colors, red (in protanopes) and green (in deuteranopes) give sensations such as would result from equivalent quantities of gray or black. As a consequence of such anomalies, pale colors within the neutral range and certain shades of red and green or compound colors containing one or other of these, are confused (*confusion colors*). The dichromat matches pale green with grays, buffs and straw colors, as well as with pale green. The red-blind also confuses yellows with greens, a bluish pink (rose color) with pale blue or violet and dark reds with dark browns, greens or blues. Red-blind persons show, as a rule, a certain degree of red-green blindness as well.

The luminosity curve (p. 958) of the light adapted eye of dichromats differs from the normal, the maximum luminosity being nearer the blue end of the spectrum (about λ 585 m μ) in protanopes and nearer the red end (about λ 600 m μ) in deuteranopes (fig. 419). The luminosity curves of the dark adapted eye of dichromats and of normal persons are identical. Owing to the absence of color at the neutral point persons with dichromatic vision can detect smaller differences in luminosity than can those with normal vision. This serves the dichromat in discriminating between certain

colors which otherwise would be confused; actually, as a result of the improvement in this faculty, some 140 different hues can be differentiated by such persons—the number for the normal eye is only about 160.

About 4 per cent of males and 0.4 per cent of females⁸ show some degree of color blindness, the great majority of these being protanopes. Both forms of anomalous trichromatism and of dichromatism are nearly always hereditary. The condition follows a mode of inheritance similar to that of hemophilia, i.e., it is a sex-linked character carried in the X chromosome (p. 94 and p. 743). As mentioned on page 94 hemophilia may in very rare instances occur in a girl or woman should her father be a bleeder and her mother a transmitter. This also applies to color blindness which, owing to the more frequent occurrence of the condition as compared with hemophilia, accounts for the 0.4 per cent of females affected.

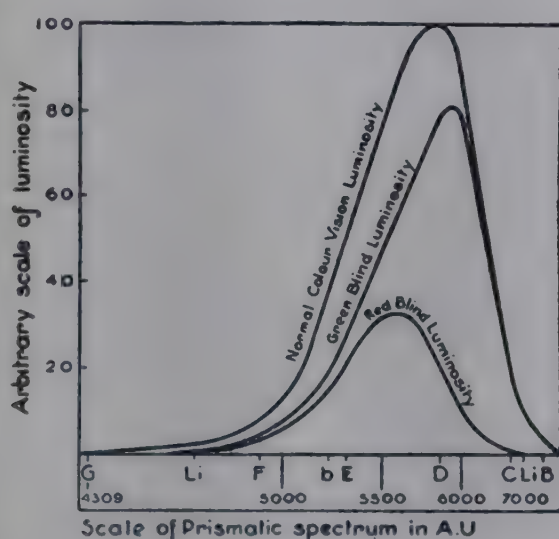


FIG. 419. Photopic luminosity curves of dichromats (protanopes and deuteranopes) compared with the normal trichromat. (After Abney.)

Tritanopia is nearly always acquired, i.e., due to some eye disease affecting the function of the rods, such as, detachment of the retina; yellows and blues are confused. The condition is simulated in jaundice because the blue rays are absorbed by the yellow bilirubin which stains the conjunctivae and ocular media. For a similar reason it is also seen as a temporary condition following the ingestion of a large dose of santonin.

Monochromatic vision or total color blindness is extremely rare. In a sense it may be looked upon as the converse of night blindness in that the function of the rods is unimpaired, but the color sensitivity of the cones is lost. To a person with monochromatic vision the surroundings appear as they do to one with normal vision at twilight, namely, in black, grays and white tinged with blue (blue sensation of the rods). The spectrum shows as in normal scotopic vision, maximal luminosity at about λ 535 $m\mu$.

⁸ Some authors (e.g., Waaler) gives figures as high as 8 per cent for males and 0.4 per cent for females.

TESTS FOR COLOR BLINDNESS. When one remembers the important part played by red and green—the two colors which are most commonly confused—in the control of our rapid transportation systems it is unnecessary to stress the dangers of defective color vision in operators, e.g., signal men, engine drivers, and seamen. In all civilized countries, applicants for employment in the marine and railway services must pass rigid color tests. Subjects of color blindness may be quite unaware of their defect, for they have no means of comparing their actual sensations with those of normal persons. They have learned to associate their own visual sensations with certain common names, e.g., red, green, etc., but unless their peculiarity is brought home to them by some glaring error, e.g., wearing a red tie to a funeral, they may not realize that the sensation which they know as red is not the same as that experienced by others. For this reason dichromats can usually name ordinary colors correctly and depend upon their power of fine discrimination between differences in luminosity to distinguish two colors which in hue appear to them alike.

Three types of test will be described.

(1) *Spectroscopic.* In this method the extent of spectral visibility,⁹ the discrimination between the different hues, the position and extent of the neutral band and the region of maximal luminosity are investigated. The determination and comparison of the ratio of red and green required to produce a homogeneous yellow (Rayleigh test) has been mentioned (p. 979). (2) *Matching.* One of the oldest and best of the methods is Holmgren's (1877) wool test. The examinee is given a set of colored wools among which are a number of so-called confusion colors. He is asked to select from the group those which match a separate wool of a specified color. In the first stage of the test the separate wool is a pale green. If he is red or green blind he matches it with cream, buff, dove gray, pale brown and straw-colored samples. He is next given a rose pink wool to match; if he chooses violet and blue wools he is red-blind, if greens, reds and browns he is green-blind. As a final test he is handed a red skein; the protanope chooses from the mixed wools dark greens and browns, the deuteranope pale greens and browns. (3) *Pseudo-isochromatic diagrams.* Ishihara's is the most satisfactory test of this type. The test comprises a series of cards upon each of which a colored field (pale green, rose, red, etc.) is printed in spots of different sizes. A

⁹ Roaf found in the investigation of twenty-four red-blind persons that the shortening of the red end of the spectrum varied considerably. In some, the red color extended to λ 620 $m\mu$, in others to λ 580 $m\mu$ and in a third group spectrum was colorless beyond only λ 480 $m\mu$.

letter or figure, also made up of spots, is outlined against the general field; these spots are of a color likely to be confused with that of the field. The subject is asked to name the figure or letter; it stands out clearly to the normal eye but to the color blind may be indistinguishable from the background.



FIG. 420. Illustrating contrast (Hering). Observe through tissue paper.

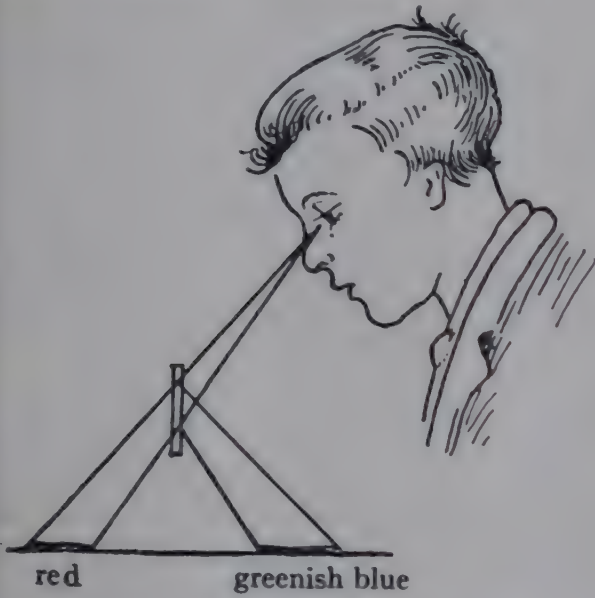


FIG. 421. Description in text.

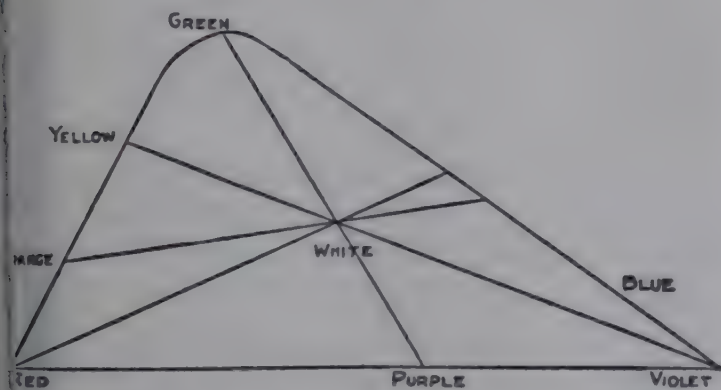


FIG. 422. Color diagram showing complementary colors.

CONTRAST EFFECTS. It is well known that when black is placed against white or vice versa they "set one another off", the black looks blacker and the white a purer white than if either were placed against a colored ground. Gray also appears darker against a white than against a black ground (fig. 420). It is also true that blue against yellow ground (or yellow against a blue ground) more vivid than if placed against any other color. So, green is enhanced by red and red by green.

These phenomena are examples of *simultaneous contrast or spatial induction*.

The maximum effect of color contrast is obtained when *complementary colors* are placed side by side. Any pair of colors which when fused as lights produce white, are said to be complementary to one



FIG. 423. Optical illusion. The distance from A to B appears to be greater than that from B to C; they are the same.

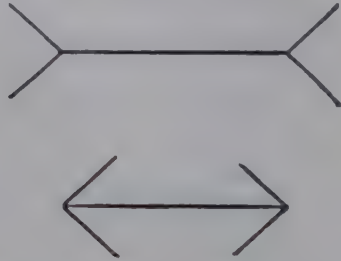


FIG. 424. Illusion of size. The vertical lines are the same length.

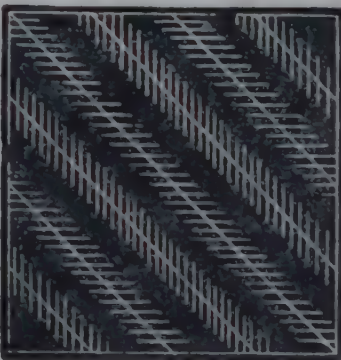


FIG. 425. Zollner's lines. The long diagonal lines appear to converge; actually, they are parallel.

another.¹⁰ Examples of complementary color pairs are the following.

- Red and greenish blue
- Orange and cyan blue
- Yellow and indigo blue¹¹
- Violet and greenish yellow
- Purple and green

¹⁰ Two sheets of paper in complementary colors (e.g., red and bluish green) or two books with their covers similarly colored are laid flat in front of the observer as shown in fig. 421. A clear glass plate is held vertically above and midway between the colored surfaces. The far surface is seen directly through the glass and the near surface by reflection. A sensation of white is caused by the overlapping of the two images.

¹¹ A distinction must be drawn here between lights and paints; we know that yellow and blue paints when mixed give green, not white. The color of a paint is due to its reflecting certain wave lengths in white light and absorbing the remainder. Even the bluest paint is not pure blue; it absorbs all light but blue and a little green. These it reflects. A yellow paint is not pure yellow; it reflects a little green with the yellow. When the two paints are mixed, blue light is absorbed by the yellow paint, and yellow light by the blue. The green rays, of which a part is reflected by each separate paint are doubly reflected when the two paints are mixed.

Not only those listed above, but every color and shade of color has its complementary (fig. 422). There are consequently a great number of complementary pairs. When a color is placed in juxtaposition to gray, the gray appears tinted with the complementary of the color. For example, a lemon or other yellow object, placed in a bright light, casts a shadow which is tinged with blue—the complementary of yellow. The shadow cast by a red object becomes tinged with greenish blue, and one cast by a purple object with green. These principles are applied in art. The artist makes a yellow flood of sunshine more brilliant by painting blue into the shadows which in turn are given depth and an appearance of reality which otherwise they would lack.

When one stares for a time at a colored surface in a strong light and then directs the gaze to a gray surface it appears tinged with the complementary color, and objects of the complementary color itself are made more vivid. For example, if one looks at a red surface for a time and then at a green one the latter color is intensified. This phenomenon is called *successive contrast* or *temporal induction*.

AFTER IMAGES. If the gaze is directed to a bright white light for a moment and the eyes then closed or turned towards a dark surface, an image of the light slowly floats into view, becomes more distinct for a time and then gradually fades. Similarly, if the eyes are stimulated by a colored light or a brightly colored object of any sort, and then darkened, an image of the same color appears. These are called *positive after images*. If, instead of closing the eyes or turning them to a dark surface after looking at a white light, the retinas are stimulated a second time and diffusely by white, e.g., by directing the eyes to a sheet of paper, one then sees a dark image against a white ground. This is called a *negative after image*. If the first stimulus was colored, then the after image is in the complementary color. Negative after images of

colored objects are the cause of successive contrast described in the last paragraph. Either the Young-Helmholtz (p. 976) theory or Hering's (p. 977) can be fitted into the phenomena of negative after images.

The adherents of the former hypothesis propose that fatigue of one or other of the three types of cone is caused by the first stimulus. Cones which have responded to a given stimulus will not for a time respond again to one of the same type. White light stimulates all three types of cone. The negative after image which appears upon applying a circumscribed and then a diffuse white stimulus to the retina is, therefore, a dark patch against a white background. When the object looked at is colored and the retina is then stimulated by directing the eyes to a white surface, the image is in the complementary color because only those cones which had not been previously stimulated can respond. For example, if the object looked at is red, the red-sensitive cones are not excited by a subsequent stimulus of white; those sensitive to green and to violet alone respond, giving a sensation the complementary of red, namely, a bluish green.

According to Hering's view the first stimulus causes catabolism or anabolism of the particular substance (red-green, yellow-blue, etc.) concerned; the opposite reaction therefore occurs upon a second stimulus and proceeds until equilibrium becomes established.

Positive after images are apparently due to chemico-physical changes in the receptors of the retina caused by and outlasting the stimulus—a form of visual persistence.

OPTICAL ILLUSIONS. The brain may be deceived by imitations of certain effects upon which our visual judgments of the size, shape and distance of objects are based. Visual errors of this nature are called optical illusions or optical deceptions. Some interesting examples are shown in figs. from 423 to 425.

CHAPTER LXXVI

THE DIPOTRIC MECHANISMS OF THE EYE. CATARACT. OPTICAL DEFECTS. INTRA-OCULAR FLUIDS

PRINCIPLES OF REFLECTION AND REFRACTION. DEFINITIONS AND TERMINOLOGY

Light falling upon a surface undergoes *absorption* and *reflection*, and, if the material is transparent, the rays are transmitted through it, either with or without *refraction*.

The proportions of rays falling upon an opaque rough surface which undergo absorption and reflection, respectively, vary with the character of the surface. A large part of the rays striking a dull white surface, e.g., a sheet of paper, are reflected but, being thrown off at different angles to the perpendicular, they do not meet at a focus in front of, or, if continued backwards, behind the surface. The light reflected from such a surface is said to be *diffuse*.

The greater proportion of the light striking a polished surface (e.g. a mirror) is reflected, but *the incident and reflected rays are always in the same plane and the angles (angles of incidence and of reflection) which they make with the perpendicular are equal*. This statement is true for any polished surface whatever its shape (fig. 426).

Reflected rays from a plane mirror are divergent; if continued backwards they would meet at a point situated at the same distance behind the mirror as the object emitting the light lies in front of it. The eye placed in the path of the reflected rays projects them to this point, where a *full-sized erect image* is formed (fig. 427). Since the rays do not actually meet at this point but only appear to do so, the image is called *virtual*.

THE FORMATION OF IMAGES BY SPHERICAL MIRRORS. A spherical mirror is the segment of a sphere; its reflecting surface may be *concave* or *convex*; its *center of curvature* is the center of a sphere of which the reflecting surface forms a part. The middle point of the surface is called the *pole* of the mirror and a line passing through the pole and the center of curvature is termed the *principal axis*. The radius of the mirror is the distance from the pole to the center of curvature. Since the latter may lie on the same side as the source of light (concave mirror) or on the opposite side (convex mirror) the radius may be *positive* or *negative*, respectively.

Rays of light coming from a distant object, i.e., from infinity, are *parallel* (1 and 2, fig. 428), falling upon a *concave mirror* they are reflected as converging rays and meet in front of the mirror at a point (F) on the principal axis (p-o). This point (F) is the *principal focus* and the distance from it to the reflecting surface is the *focal length* or *focal distance* of the mirror. A *real*

inverted image of the object and *smaller* than it, is formed in the air at the principal focus. The rays from a near object are divergent; the reflected rays are therefore less strongly convergent than when the incident rays are parallel. If the object is at the

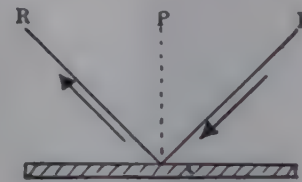


FIG. 426

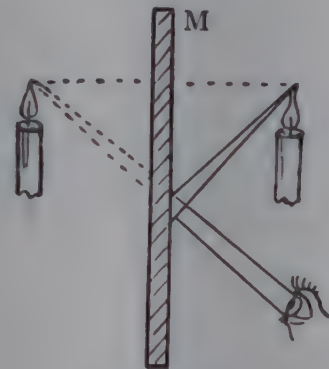


FIG. 427

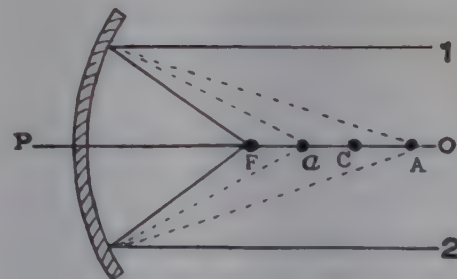


FIG. 428

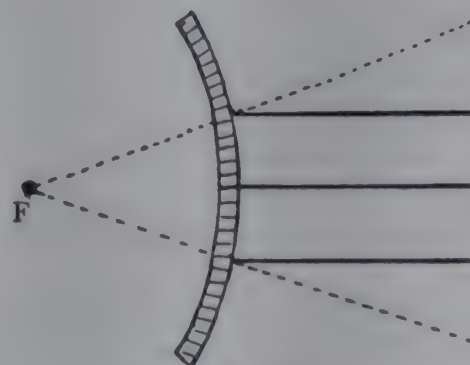


FIG. 429

center of curvature (C) of the mirror then the rays are reflected back to this point and no image is formed. When the object is at *a* between the center of curvature of the mirror and the principal focus, its image is at A beyond the center of curvature; when the object is

beyond the center of curvature (at A) its image is between the latter and the principal focus, i.e., at *a*. These two points are therefore reciprocally related and are called *conjugate foci*. An object placed between the mirror and its principal focus emits rays which upon reflection are widely divergent and cannot be brought to a focus in front of the mirror. Projected backwards they meet a point behind the mirror where a *virtual erect* and greatly *enlarged* image is formed.

Parallel rays striking a *convex mirror* are reflected as *divergent* rays which to the eye appear to come from a point behind the mirror—the *principal focus* (F). Here a *virtual erect image*, smaller than the object, is formed (fig. 429).

REFRACTION. Rays of light in passing obliquely from one transparent medium to another of a different optical density (e.g., from air to glass) are bent or refracted. If one medium is surrounded by the other (e.g., glass in air) the ray is refracted twice. In passing from the medium of lower to the one of higher optical density the rays are bent towards the perpendicular;¹ in the transition from the denser to the rarer medium the bend is away from the perpendicular. With any two media the greater the obliquity of the incident rays the greater is the degree of refraction; rays perpendicular to the surface between the two media are not refracted. The ratio of the angle made by the incident ray (i.e., the ray falling upon the surface of the second medium) with the perpendicular (angle of incidence) to that made by the emergent ray (angle of refraction) is termed the *refractive index* or the *index of refraction* of the material in question. The refractive index is therefore a measure of refractive power. The refractive index of air being taken as unity, that of water is 1.3 and of ordinary glass 1.5.

Refraction by plane surfaces. Oblique rays striking a medium with plane parallel surfaces, such as a sheet of glass, are refracted to an equal degree upon entering and emerging through in opposite directions, i.e., towards and away from the perpendicular, respectively. The incident and emergent rays are therefore parallel though not quite in the same straight line (fig. 430). A *prism* has its sides inclined towards one another. Since a ray is refracted upon entering at one surface of the prism and again upon emerging at the other, and is bent nearer to the perpendicular in the former instance and away from the perpendicular in the latter, it will be refracted each time towards the base of the prism (fig. 431).

Lenses are of two main types, *spherical* whose surfaces are the segments of spheres and *cylindrical*. There are six varieties of the former—*planoconvex*, *biconvex*, *planoconcave*, *biconcave* and two *meniscus lenses*—*converging* and *diverging* (see fig. 432).

Convex lenses may be looked upon as a great number of truncated prisms with their bases directed towards the lens center. Concave lenses, on the other hand,

are as a number of prisms arranged with their base towards the periphery (fig. 433). It follows then that a symmetrical biconvex lens will bend rays to the same degree at equal distances from its center and bring

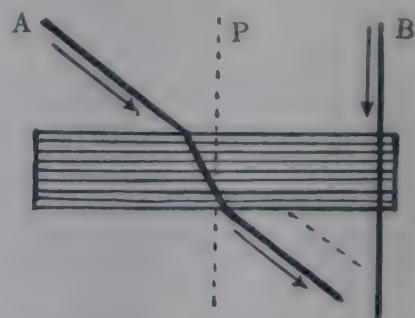


FIG. 430. The oblique ray (A) is refracted upon entering and leaving the block of glass. The emergent ray has the same direction as the entering ray but is not in the same line. P represents perpendicular. The ray B which strikes the glass surface perpendicularly is not refracted.

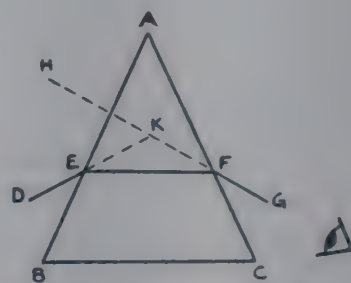


FIG. 431. ABC is a prism with the apex at A, the base BC, and the sides AB and AC. The angle of the prism is BAC. A ray of light DEFG is refracted at E and F as in figure 435. The total amount of refraction that is, the difference in direction between DE and FG, is represented by the angle DKH (the angle of deviation). If the eye is at G, the source of light, D, will appear to be at H. When the ray passing through the prism (EF) is parallel to the base (BC), the ray is said to traverse the prism symmetrically.



FIG. 432. Cross sections of lenses. *a*, planoconvex; *b*, biconvex; *c*, concavoconvex; *d*, planoconcave; *e*, biconcave; *f*, convexoconcave.



FIG. 433. See text.

them to a meeting point or focus, whereas concave lenses will cause divergence of the rays. In either instance the rays are bent towards the bases of the constituent prism.

¹ That is, they become more perpendicular.

Refraction by convex lenses. A line passing through the centers of curvature of the lens is termed the *principal axis of the lens*. Any other line intersecting the principal axis within the lens (i.e., a diagonal line) is called a *secondary axis*. The *radius of curvature* of the lens is the radius of a sphere of which the refracting surface forms a part. Rays passing through the principal axis are not refracted, for the incident and the emergent ray strike each surface perpendicularly and the two surfaces at these points are parallel (see above). Moreover, rays in the secondary axes undergo only very slight refraction and the incident and emergent rays, though not quite in a continuous line, are parallel, for again the surfaces which they pierce are parallel. The point where the principal axis is intersected by the secondary axes is termed the *optical center* or *nodal point* of the lens. In a biconvex lens with symmetrical surfaces the actual and the optical centers coincide, but in other biconvex lenses the nodal point may be situated nearer to one or other surface.

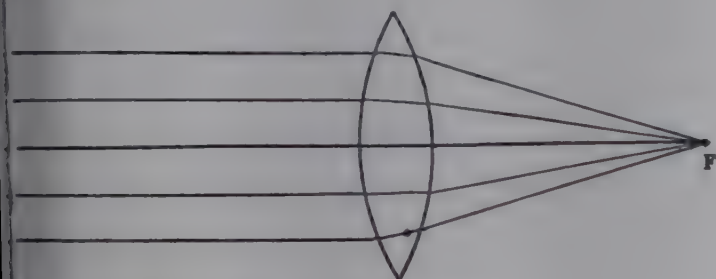


FIG. 434. See text.

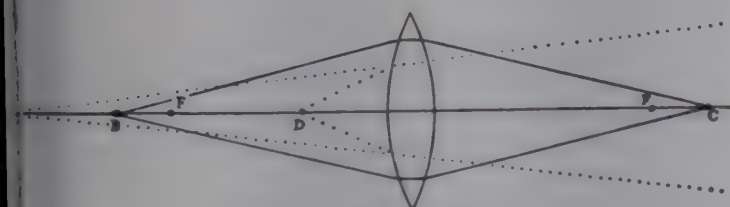


FIG. 435. See text.

Light rays from a *distant object*, i.e., from infinity, are parallel (fig. 434). The point F where parallel rays meet after refraction is called the *principal focus*. The distance of this point from the lens is called the *focal length* or *focal distance of the lens*. The rays of a light placed at the principal focus traverse the same path but in the opposite direction, and emerge as parallel rays.

A *near object* emits divergent rays. If the source of light (fig. 435, B) is on the principal axis a little beyond the principal focus, an image is formed at a distance on the other side of the lens greater than its focal length (at C); when the object is placed in the second position (D) an image is formed at the first (B). These points are therefore, in respect to an object and its image, are interchangeable and are termed *conjugate foci*. If the object is situated at a distance exactly double the focal length of the lens the conjugate foci are at equal distances on the two sides of the lens. In all these instances a *true inverted image*, smaller than the object, is

formed. If the source of light (D) lies between the lens and its principal focus, the rays, after passing through the lens, are widely divergent. To the eye placed in the path of the emergent rays they appear to come from a point (V) at a greater distance behind the lens than the actual. A *virtual, erect and enlarged image* is formed.

Light rays in passing through a *biconcave lens* are diverged (fig. 436), therefore a *true image* is not formed. The eye in the path of the rays takes no account of refraction and the rays in consequence are projected backwards as straight lines which, meeting at a point

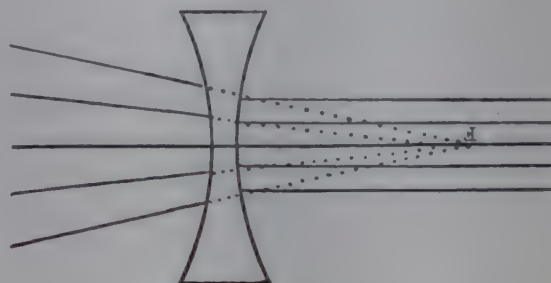


FIG. 436. See text.

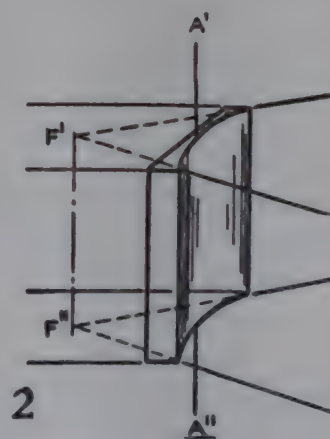


FIG. 437. 1, refraction by a convex cylinder. A point of light is brought to a focus as a line after refraction through a cylinder. 2, refraction of light by a concave cylinder. Rays of light striking the cylinder perpendicularly to the axis A'A" are diverged, and appear to be brought to a virtual focal line F'F" (After Duke-Elder.)

on the other side of the lens, form a *virtual erect image*, smaller than the object.

Cylindrical lenses (fig. 437) have one plane surface, the other may be *convex* (*convex cylindrical lens*) or *concave* (*concave cylindrical lens*). A convex cylindrical lens may be regarded as a section of a cylinder sliced down its long axis; its horizontal meridian is convex. Rays transmitted through it at right angles to its vertical axis are converged as they would be by a convex spherical lens. Light traversing its long axis is not refracted, the lens acting in this axis as a plate with parallel sides. A lens of this type may be looked upon

as an infinite series of prisms arranged base to base in tiers. In the other type of cylindrical lens the horizontal meridian is concave; rays passing at right angles to the vertical axis are diverged.

THE REFRACTING MEDIA OF THE EYE. These are the cornea, the aqueous humor, the crystalline lens and the vitreous body. The refractive indices are given in the following table.

Cornea	1.34
Aqueous humor.....	1.33
Crystalline lens (whole).....	1.42
Vitreous body.....	1.33

It will be noticed that the refractive indices of the cornea and the aqueous humor are approximately the same; for practical purposes they may be taken as identical and the two be regarded as a single refracting medium. The eye, then, has three refracting surfaces, (a) the anterior surface of the cornea, (b) the anterior surface of the lens and (c) the posterior surface of the lens. The greatest refraction occurs at the corneal surface (42 diopters); of less importance is refraction at the surfaces of the lens (19 diopters with accommodation relaxed and 36 diopters in full accommodation). The value in the table above for the refractive index of the lens is calculated from the refractive power of the lens as a whole, as though it were a homogenous structure, but such is not the case. On the contrary, the lens consists of an almost spherical *nucleus* with a high refractivity (1.41) surrounded by a zone called the *cortex* of lower optical density (1.38). The surrounding cortex is composed of a series of concave meniscus lens, as shown in fig. 438. Thus an image formed by the anterior part of the cortex (B) is focussed by A and the second image in turn by C. The peculiar structure of the lens accounts for the apparent paradox that the mean value of the refractive indices of its parts (1.39) is less than the refracting power of the whole. Several important advantages are derived from this peculiar structure of the crystalline lens; it diminishes spherical and chromatic aberration (p. 1000), tends to prevent the scattering of light within the eye and enhances the power of the lens to alter its converging power during accommodation (p. 995).

The diopter. The converging or the diverging power of a lens depends upon the curvature of its surfaces (the greater the degree of curvature, the greater the refracting power) as well as upon the refractive index of the material of which it is composed. The focal length of a lens varies inversely with the refractive power and is therefore a convenient measurement for expressing

the strength of a lens. The standard focal length taken as 1 meter. The refracting power is expressed the reciprocal of the focal length, the unit being *diopter* (abbrev. D). Thus, the strength of a lens with a focal length of 1 meter is 1 diopter; of one with a focal length of 2 meters, $\frac{1}{2}$ a diopter; of one having a focal length of $\frac{1}{2}$ a meter, 2 diopters, and so on. The symbols + or - (+1 D, +2 D, -1 D, -2 D, etc.) are used respectively for a converging and a diverging lens. For example, if a concave lens has a refracting power -1 D, a small virtual image of a distant object will be focussed 1 meter from the lens and on the same side as the object. A convex lens of a corresponding power (+1 D) will bring parallel rays to a true focus 1 meter behind the lens. The power of a cylindrical lens is expressed in a similar fashion.

THE CONSTANTS OF THE EYE. Knowing the curvatures of the refractive surfaces of the eye and the distances between them as well as the refractive indices of the media, the path taken by the rays of light can be determined and the image co-

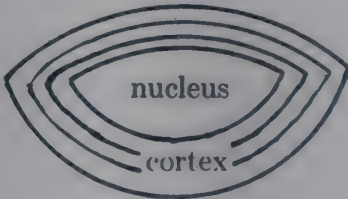


FIG. 438. Showing structure of the crystalline lens (diagrammatic).

structed. The values of the *constants of the eye* are given in the following table.

	mm.
Position of anterior surface of cornea.....	0
Position of posterior surface of cornea.....	0.6
Position of anterior surface of lens.....	3.6
Position of posterior surface of lens.....	7.2
Position of retina.....	24.1
Radius of anterior surface of cornea.....	7.7
Radius of posterior surface of cornea.....	6.8
Radius of anterior surface of lens.....	10.0
Radius of posterior surface of lens.....	6.0

The refractive indices of the media have been given above.

Construction of the image from the foregoing data is a very laborious proceeding. To start with, the image formed by the first refracting surface is constructed; this image now serves as the object for the next refracting surface, the second image in turn is the object of the third surface and so on. The matter is very much simplified, however, by constructing the *diagrammatic* or *schematic* eye by the application of the theorem of Gauss. This states that every optical system composed of spherical surfaces with their centers

on the principal axis has three pairs of cardinal points. These are, two *principal points* (K and H', fig. 439), an *anterior* and a *posterior focal point* (ϕ and ϕ') and two *nodal points* (K and K').

The *first and second principal points* lie close together in the anterior chamber 2 mm. behind the cornea. Planes passing through the principal points and perpendicular to the axis are termed the *first and second principal planes*; an object in the first principal plane forms an erect *full-sized image* in the second and vice versa. The first and second principal points correspond, therefore, to the conjugate foci of a single lens.

The anterior focal point (ϕ) is situated 15.7 mm. in front of the cornea. Rays from this point in the axis would, after passing through the system, emerge as parallel rays. Parallel rays entering the system are focussed at ϕ' which is situated on the retina. ϕ and ϕ' therefore correspond to the principal foci of a single lens (p. 985).

This has a single ideally refracting surface situated in the anterior chamber 1.35 mm. behind the cornea and with a radius of 5.7 mm. The nodal point or optical center of the reduced eye lies 7.08 mm. the principal point 2.3 mm. and the posterior focal point 24.13 mm. behind the anterior corneal surface. The anterior focal point is 15.7 mm. in front of the cornea. The distance of the nodal point from the retina, i.e., the focal length of the eye, is $(24.13 - 7.08 =) 17.05$ mm. The refracting power is therefore $\left(\frac{1000}{17.05} =\right) 58.65$ diopters.

By means of an X-ray beam, which is not refracted, projected into the eye Goldman and Hagen have measured the length of the globe in the living human subject. The value obtained (23.4 mm.) agrees closely with that of the schematic eye. The value for the total refractive power of the normal human eye, as determined by these observers, is also in close agreement, namely, 59.22 diopters.

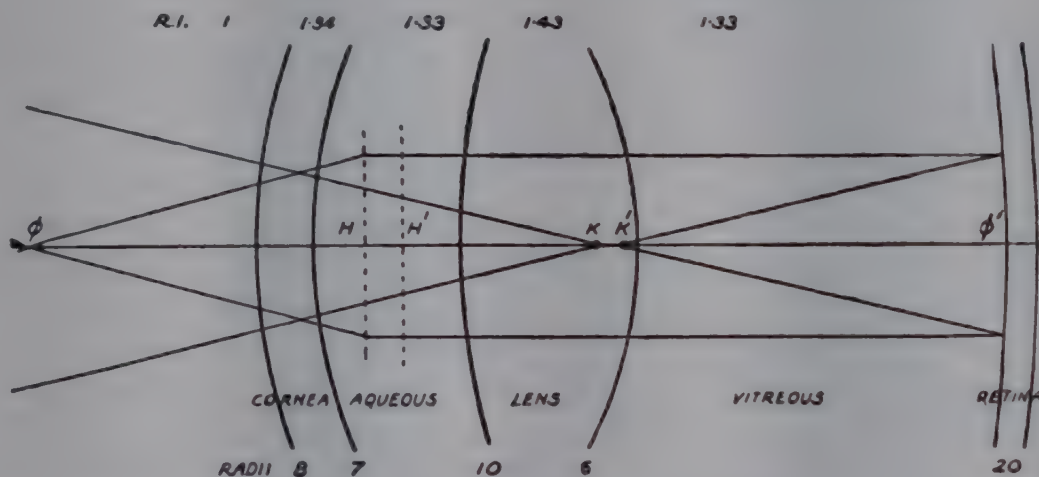


FIG. 439. The cardinal points of the eye. ϕ , The anterior focus, 15.7 mm. in front of the cornea. ϕ' , The posterior principal focus, 24.13 mm. behind the cornea—that is, upon the retina. H, H', the principal points, in the anterior chamber. KK', the nodal points, in the posterior part of the lens. (After Duke-Elder.)

The nodal points (K and K') also lie close together on the axis and near the posterior surface of the lens. They correspond to the optical center of a single lens. Rays passing through the nodal points are not refracted. A ray entering the system and passing through K appears to come from K' and emerges along a line parallel to that along which it entered. The following table for the schematic eye gives the distances of the six cardinal points from the anterior surface of the cornea.

	mm.
Anterior surface of cornea.....	0
First principal point, H.....	1.7
Second principal point, H'.....	2.0
First nodal point, K.....	7.0
Second nodal point, K'.....	7.3
Posterior focal point, ϕ	24.1
Anterior focal point, ϕ'	15.7

The two nodal points lie so close together that no significant error is entailed if they are taken as one; the same may be said for the principal points. Thus the compound optical system of the eye can be simplified to the so-called *reduced schematic eye* of Listing.

THE FORMATION OF THE IMAGE ON THE RETINA. Knowing the foregoing measurements, the paths taken by the light rays can be drawn and a construction of the image upon the retina readily carried out. The formation of the retinal image is illustrated in fig. 440. The large arrow A-B represents an object emitting divergent rays which are converted and brought to a focus to form the image represented by the small arrow a-b. The retinal image, it will be observed, is smaller than the object and inverted. For the sake of simplicity only four rays are shown, two from a point at either end of the object, but of course the surface of an object consists of an infinite number of points, each of which emits divergent rays. One of each pair of rays in the figure (solid line) passes unrefracted through a secondary axis (i.e., through the nodal point N), the ray from the upper part of the object to the lower part of the retina and vice versa. The other ray of each pair (dotted line) undergoes refraction and meets the corresponding

unrefracted ray. Similarly, rays from a point on one side of the object will fall upon the retina as a point of light in the opposite part of the image. Thus, it is seen how the image on the retina becomes inverted. Of course we see objects in their true position. Re-inversion is a cerebral function developed, probably, through the association of visual sensations with those of touch. The process itself is essentially psychological and beyond our ability to analyze.

The idea that the retinal image is inverted was at first difficult to believe. Kepler (1604) inferred from his optical studies that this must be so, but it was Scheiner (1625) who furnished the proof by observing the back of an excised eye from which the sclerotic and choroid coats had been removed. The inverted image of an object was clearly visible upon the translucent retina. The inversion of the retinal image may also be demonstrated during life in persons of blonde complexion because their choroid contains little pigment.

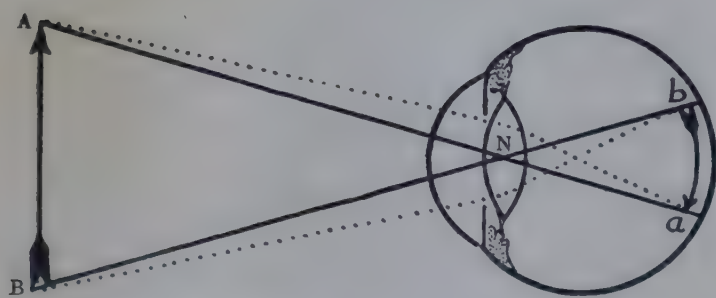


FIG. 440. Illustrating the formation of the retinal image.

The subject is examined in a darkened room, the eye being turned towards a lighted candle placed well to the temporal side. An inverted image of the flame may be seen showing through the inner side of the wall of the globe. The retinal image can be seen most readily by means of the ophthalmoscope or in the excised eye of a rabbit whose choroid is devoid of pigment.

The size of the retinal image is dependent upon the angle $a N b$, (fig. 440) this—the angle subtended at the nodal point of the eye by an object in the visual field—is called the *visual angle*. The size of the image can be calculated if one knows the distance of the nodal point of the eye from the object and from the retina, and the size of the object. Thus in the figure $A B$ is the object and $a b$ its image. The triangle $A N B$ and $a N b$ being symmetrical, then

$$a b : A B = b N : B N$$

$$a b = A B \times \frac{b N}{B N}$$

$$b N = 17.05 \text{ mm.}$$

$$i = 17.05 \times O/d$$

i is the size of the image, O the size of the object and its distance from the nodal point of the eye (17.05 = distance of retina from nodal point, see p. 987).

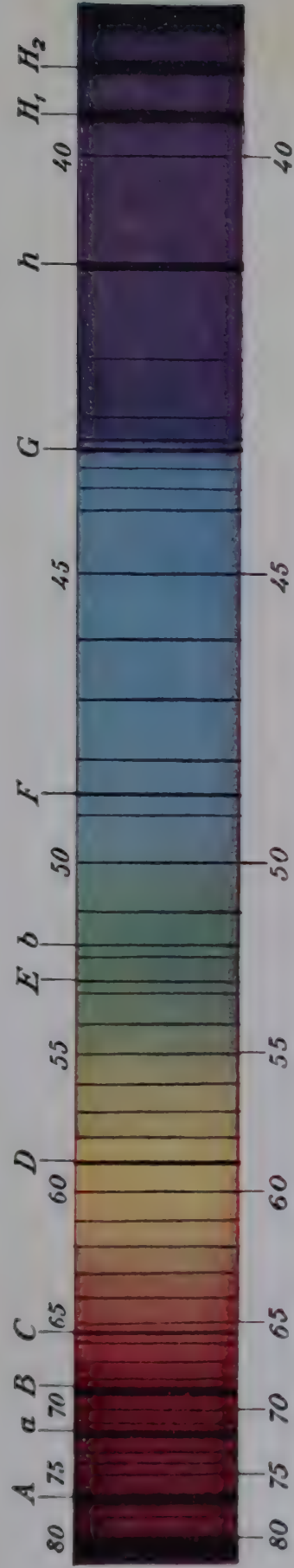
THE OPHTHALMOSCOPIC EXAMINATION OF THE EYE. Under ordinary circumstances we cannot see within the eye of another person, because only a limited quantity of light enters his eye through the relatively small pupillary aperture. It is like trying to look through a small window into a darkened room. Furthermore, the pupil constricts and, of the light which passes through the pupil a large part is absorbed by the pigment layer of the retina.² Even when a light is brought close to the eye under observation, one is unable to see the retina, because the pencil of parallel rays which emerge do not enter the examiner's pupil unless his eye is directly in its path, and when he attempts to bring his eye into the proper position either his head comes between the light and the subject's eye or the light (if between himself and the subject) dazzles his sight.

These difficulties are overcome by means of the ophthalmoscope. This instrument consists of a small mirror with a central perforation through which the observer views the subject's eye. Light furnished by an electric lamp placed above the head of the patient is reflected from the mirror and the pencil of rays emerging from the subject's eye passes through the aperture of the mirror to the examiner's eye (fig. 441).

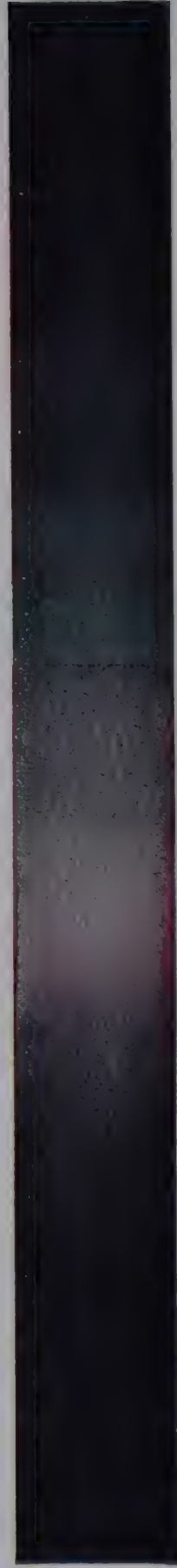
The invention of the ophthalmoscope is commonly attributed to Helmholtz (1851) but a crude device based upon the same principle was used by Babbage two years previously. The instrument consists of two mirrors, each with a central aperture. One mirror is plane, the other concave; they are pivoted so that one or other can be rotated into position as required. The obverse side of the instrument holds a series of small lenses ranging from + 30 D to - 30 D in strength, any one of which can be moved into position over the central aperture. The examiner seats himself 1 meter from the subject and looking through the peephole of the plane mirror reflects a beam of light into the eye. If the observed eye is emmetropic a uniform red glow—the *red reflex of the fundus*—caused by reflection from the retina is seen lighting up the pupil. No detail.

² The red glow seen in the eyes of certain animals, especially of the cat and other carnivora, is due to the presence of a highly polished area at the fundus—the *tapetum lucidum*—which acts as a concave mirror to throw back a large proportion of the light which enters the eye. This structure lies behind the retina, the pigment layer being absent over it. It is composed of several layers of flattened endothelial cells overlain with doubly refracting crystals.

PLATE 1



Spectrum as seen by light adapted eye (Photopic vision). (Figures from Duke-Elder *Text-book of Ophthalmology*, by permission of Henry Kimpton, London.)



Spectrum as seen by the dark adapted eye (Scotopic vision).

PLATE 2



Normal Human Fundus. (From May's *Manual of Diseases of the Eye*, by permission of the author.)

e.g., optic disc or retinal vessels, is visible because the rays emerging from the subject's eye are in two parallel beams which soon diverge and cannot be brought to a focus upon the observer's retina. On the other hand, if the eye is hypermetropic or myopic an image is formed. In the former state the emergent rays are divergent and appear to meet behind the eye where a virtual, erect image of the retina is formed. In myopia the emergent rays are convergent and, meeting in front of the eye, form a true inverted image.

After this preliminary examination one or other of two methods of ophthalmoscopy—the indirect or the direct—may be employed. In both methods the concave mirror is used. In the *indirect method* a separate biconvex lens with a focal length of 7.5 cm. (about 13 D) is held in front of the eye of the examinee. The observer seats himself 1 meter away and holds the lens in the path of the beam from the mirror and a short distance in front of the eye under observation. The pencil of parallel rays emerging from the subject's eye will be brought to a focus by the biconvex lens; a highly magnified, real and inverted image is formed in

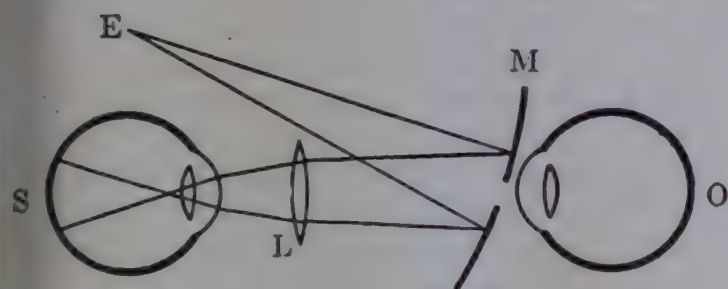


FIG. 441. Illustrating the principles of the ophthalmoscope. E, light; L, lens; M, mirror; O, observer; S, subject.

the air at the principal focus of the lens, i.e., between it and the examiner. The subject turns his eye a little inwards in order to bring the optic disc into view, being directed, for example, to look at the observer's left ear if his left eye is being examined. By moving the lens towards or away from the subject's eye a point is reached where his retina is brought into focus and the optic disc with its vessels (Plate II) clearly seen. In the *normal* eye the image is formed as follows. The diverging rays from the light are reflected from the concave mirror along converging lines. The rays are converged further in passing through the biconvex lens and the refracting media of the eye and are brought to a focus on the patient's retina (fig. 441). Upon reflection from the fundus they emerge from the eye along parallel lines; they are next converged by the biconvex lens and, as mentioned before, form a large inverted image in the air (see fig. 442 A). In the *hypermetropic* eye the emergent rays are divergent. They appear therefore to come from a point behind the eye where a large, erect virtual image is formed. The lens, using this as object forms a small inverted image of it at a greater distance in front of the lens than its focal

length (fig. 442 B). In myopia the emergent rays are convergent and will form an inverted image of the retina at $\alpha\beta$ (fig. 442 C). The biconvex lens forms of this a final small image $a b$ within its own focal length.

In the *direct method* a field of smaller area but of higher magnification is seen. The light is placed behind the patient's head and to one or other side, depending upon the eye to be examined. The examiner comes quite close to the subject and without the aid of a biconvex lens observes the fundus (right fundus with his own right eye, and left fundus with his left eye). The small concave mirror, which is set obliquely in the in-

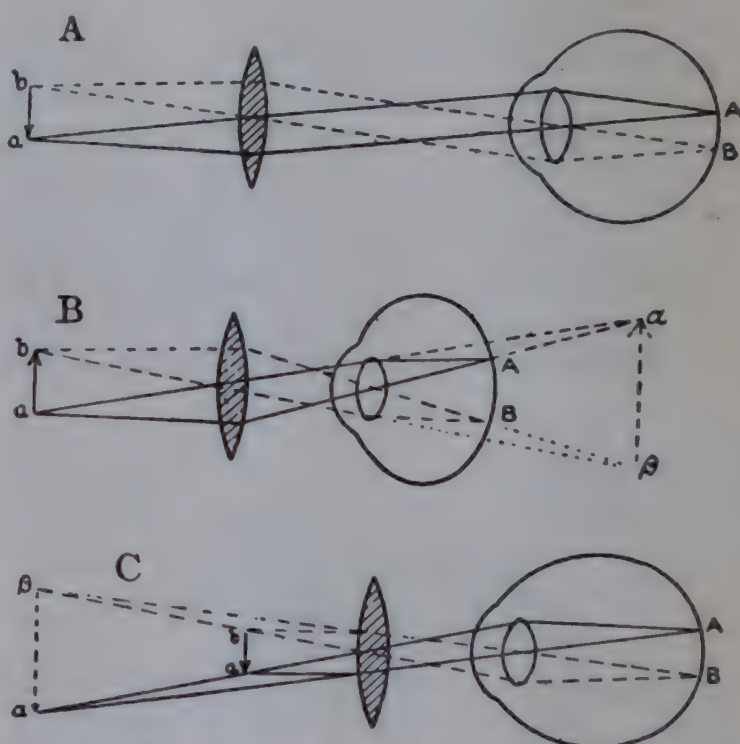


FIG. 442. A, path of the light from the eye in the indirect method of ophthalmoscopy in emmetropia. AB , the illuminated area on the retina, gives an image, ab , in the air on the side of the condensing lens farthest from the eye. B, path of the rays of light from the eye in indirect ophthalmoscopy in hypermetropia. AB , the illuminated area on the retina gives an imaginary image $\alpha\beta$ behind the eye. This is focused in a final image at ab by the condensing lens. C, path of the rays of light from the eye in indirect ophthalmoscopy in the myopic eye. AB , the illuminated area on the retina, forms an inverted aerial image in front of the eye at $\alpha\beta$. The condensing lens gives a final image (ab) situated within its own focal length. (After Duke-Elder, *Text Book of Ophthalmology*.)

strument, is rotated to the proper angle to throw a reflected beam through the pupil. The light, after coming to a focus on the retina, emerges from the emmetropic eye as parallel rays which are brought to a focus upon the observer's retina. If, however, the subject's eye is hypermetropic (p. 1001) the emergent rays will be divergent and can only be focussed by the examiner if he accommodates his eye or interposes a convex lens; if the observed eye is myopic the reflected rays are convergent; the examiner must then use a concave lens in the order to focus the image upon his own retina.

Papilledema (choked disc, optic neuritis) and optic atrophy. In conditions accompanied by high intracranial pressure, e.g., brain tumor, hydrocephalus and uremia, the optic disc loses its natural translucency and becomes reddened and swollen. The central vein is engorged and tortuous and the venules and capillaries dilated. Small hemorrhages may be seen. The swelling of the disc is due to the transudation of fluid from the engorged vessels and its collection in the anterior layers of the lamina cribrosa and between the nerve fibers. The physiological cup becomes gradually filled up, and may eventually be elevated above the general level of the surrounding retina. The circumference of the disc ill-defined, appearing blurred or "woolly." The disc is enlarged and its lateral spread causes the retina to be thrown into folds or ridges. In the older terminology these changes were referred to as choked disc, optic neuritis or papillitis. The condition is now called *papilledema*. The separation and stretching of the nerve fibers, their compression where they penetrate the lamina cribrosa and the overgrowth of glial tissue set up by the presence of the edema fluid leads to nerve atrophy—*secondary optic atrophy*. The disc in this

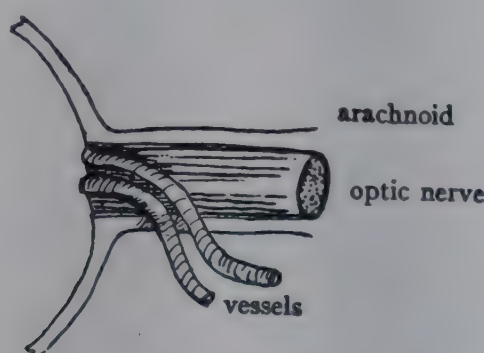


FIG. 443. Description in text.

condition is a grayish or dead white, due to the obliteration of capillary vessels by the overgrowth of glial tissue. The optic cup is deepened as a result of the degenerated nerve fibers. The outline of the pale disc is clearly defined against the surrounding retina. The retinal veins are engorged but the arteries are narrower than normal.

It is now almost universally agreed that mechanical factors alone are concerned in the production of papilledema. The optic nerve, it will be recalled, is invested by prolongations of the cerebral meninges—the *pia*, *arachnoid* and *dura*. The spaces between these three layers of the nerve sheath—the *subarachnoid* and *subdural spaces*—are continuous, as was first shown by Schwalbe (1870) with the corresponding spaces within the cranium. The *dura* and *arachnoid* of the nerve sheath, however, are in close opposition, there being only a potential subdural space in this situation. But the intracranial subarachnoid space is in free communication with the corresponding space of the nerve sheath and the intracranial pressure is transmitted through the cerebrospinal fluid to the intravaginal space right up to the lamina cribrosa. The central vein of the

retina with its companion artery makes an almost right angled bend as it leaves the optic nerve and, crossing the intravaginal space, pierces the arachnoid and dissects a short distance behind the eyeball (fig. 443). A marked rise in intracranial pressure distends the sheath for the *dura* in this situation differs from that within the cranium in being unsupported by bone (Macdonald). The elevated pressure thus transmitted to the sheath tends to compress the vein in its course across the intravaginal space and to impede the venous return as well as to block the lymph channels situated in the adventitia of the central vessels. Little or no interference is offered to the blood flow in the artery owing to its more resistant wall and to the higher arterial blood pressure. The venous pressure rises and the intraocular part of the vein and its branches become engorged since they are beyond the influence of the intracranial pressure.

Papilledema is therefore comparable with an edema which may occur in almost any situation as a result of obstruction of the venous and lymphatic channels while the arteries remain pervious. No evidence that papilledema is inflammatory in nature can be found upon histological examination (Holmes and Paton). The theory that high intracranial pressure causes edema of the disc by raising the pressure in the cavernous sinus (which receives blood from the central vein either directly or through the superior ophthalmic vein) is controverted by the following facts. (a) The central vein of the retina after piercing the *dura* anastomoses with the orbit with one or other of the ophthalmic veins (usually the superior) and through it with the pterygoid venous plexus and the facial vein. Thus an alternative system of channels is provided for the drainage of blood from the retina. (b) Ophthalmic changes are not seen as a rule in thrombosis of the cavernous sinus.

It has been suggested by Macdonald that cases of retinal detachment which sometimes follow a powerful straining effort (e.g., lifting a heavy weight) may be due to an acute retinal edema caused by the sharp rise in intracranial pressure which such acts induce. In this view the distension of the nerve sheath by cerebrospinal fluid causes the central vein to be bent more acutely at the point where it leaves the nerve and that the venous congestion is caused in this way rather than by pressure upon the vessel in its subarachnoid course.

Atrophic changes in the disc occurring unpreceded by papilledema are referred to as *primary optic atrophy*. The main causes of primary optic atrophy are pressure upon the nerve within the cranium as by a tumor, certain nervous diseases (tabes, general paralysis of the insane and disseminated sclerosis) and toxic substances, e.g., wood alcohol, quinine, lead and salicylic compounds. Since the optic nerve fibers have their cell bodies in the retina (ganglion cell layer) the atrophy of the section between the point of pressure and the retina is in the nature of a retrograde degeneration (p. 779). As already mentioned on page 779, the optic nerve is devoid of a neurilemma; regeneration

therefore never occurs. In tabes and general paralysis of the insane the atrophy is probably the result of a syphilitic meningitis which affects the nerve secondarily. The toxic substances mentioned exert their action apparently directly upon the ganglion cells of the retina.

RETINOSCOPY OF SKIASCOPY. This is a reliable objective method for determining the refraction of the eye. It is of special value in children and others for whom the reading of test type is impracticable, and for the detection of malingerers. The test, which will now be described, was first employed by Cuignet (1873). When a lighted candle is placed in front of the eye the rays are brought to a focus or a partial focus upon the retina. Since the retinal image is inverted, a movement of the candle to one side causes the illuminated area on the retina to move in the opposite direction. Rays from the candle or other luminous object reflected from a plane mirror form a virtual image behind the reflecting surface (p. 983). Tilting the mirror to one or the other side causes this image to move in the opposite direction. Consequently, when the reflected light is thrown into the eye by means of a plane mirror, owing to a double reversal of the movement taking place (i.e., a movement of the mirror image which now serves as the luminous object in one direction and of the retinal

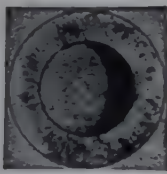


FIG. 444. Retinoscopy shadow. (After Duke-Elder.)

image in the other), a change in the inclination of the mirror causes the illuminated area upon the retina to move in the *same* direction as the tilt. This movement of the illuminated area on the retina in relation to the tilt of the mirror is the same whatever the refractive state of the eye. But the rays from the illuminated area on the retina are reflected back through the pupil and undergo refraction; the appearance of the image of the light to the eye of the observer depends upon the direction of the emergent rays.

If the eye is *emmetropic* or *hypermetropic*, or *myopic* to a degree less than $-1D^3$ the image is seen by the observer as a bright area bounded by a faint shadow with a vertical (straight) border (fig. 444). In degrees of myopia greater than $-1D$ the shadow is deeper, more clearly defined and has a concave edge. In myopia of $-1D$ no shadow is seen, the pupil is either uniformly illuminated or entirely dark. As the mirror is tilted the direction, rate and excursion of movement of the shadow varies according to the refractive state of the eye. In emmetropia, hypermetropia and degrees of myopia less than $-1D$ the image moves *with* (i.e., in the same direction as) the tilt of the mirror. In

degrees of myopia greater than $-1D$ the image moves *against* the mirror (fig. 54 A). With a myopia of $-1D$ the two opposite movements are neutralized and, as mentioned above, no definite line of shadow can be observed. At this point—the so-called *point of reversal*—a weak concave or convex lens placed in front of the subject's eye causes the shadow to reappear and to move, respectively, *with* or *against* the tilt of the mirror. These facts are explained as follows. In myopia the emergent rays are convergent and form an inverted image in the air at the far point of the eye (p. 1000). Since, as mentioned above, the illuminated area on the retina in all instances moves with the mirror the inverted image must move against it when the myopia is greater than $-1D$ and the observer is placed a little more than 1 meter distant, i.e., the image is formed

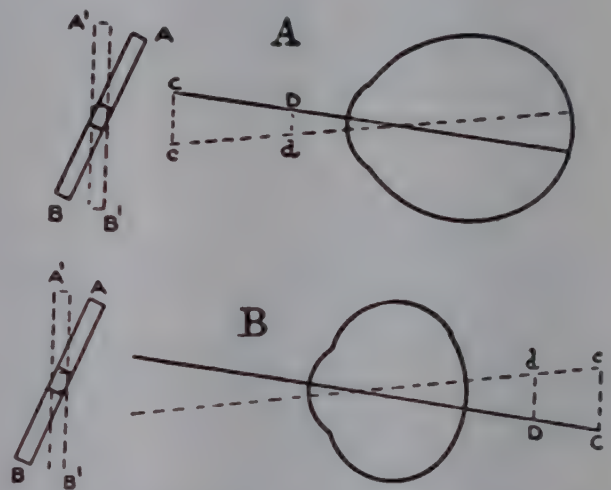


FIG. 445. Illustrating the movements of the shadow in retinoscopy. A, in *myopia*. When the mirror is in the position AB, the image is at D in the highly myopic eye, and at C in the less myopic eye. When the mirror is in the position A'B', the respective images are in the positions *d* and *c*. Since *Dd* is less than *Cc*, the lower the degree of myopia, the larger the excursion and the quicker the movement of the shadow. B, in *hypermetropia*. When the mirror is in the position AB, the image is at D, in the highly hypermetropic eye and at C in the less hypermetropic eye. When the mirror is in the position A'B' the respective images are at *d* and *c*. (After Duke-Elder, *The Practice of Refraction*.)

between the subject and the observer. It will be clear from fig. 445 that the higher the degree of myopia, i.e., the closer the far point of the subject, the slower will be the movement and the smaller its excursion. In myopia less than $-1D$ the emergent rays meet and form an image at a distance greater than 1 meter, i.e., the observer's eye is situated closer to the subject's eye than its anterior focal distance. The shadow therefore moves *with* the mirror.

In hypermetropia the emergent rays diverge and appear to come from a point behind the subject's eye; here an apparent erect image is formed. The shadow, therefore, as shown in figure 445 B, moves with the mirror, its speed being slower and its excursion smaller the greater the refractive error. The point of reversal occurs when the far point of the subject and the ob-

³That is, $-1D$ would be required to correct the error.

server's eye coincide. Therefore, at the usual distance at which the examiner is seated, this occurs when the myopia amounts to -1 D. The far point of the emmetropic eye is at infinity, therefore reversal in such an eye occurs should the observer place himself at a distance of 20 feet or more from the subject, i.e., at infinity.

The presence and the degree of a refractive error is determined in the following manner. The observer is seated at a distance of 1 meter from the eye to be observed. Light from a source above the subject's head is reflected into his eye by means of a plane mirror with a central aperture, and the appearance and movements of the shadow noted. If the pupil is uniformly illuminated or black but no definite shadow is discernible, the eye has a myopia of -1 D. Should a shadow be present and it moves *with* the mirror the eye is either emmetropic, myopic to a degree less than -1 D or hypermetropic. Convex lenses are then added until the shadow disappears (point of reversal): a slightly stronger lens ($+0.25$ D) is then added, which should cause a movement opposite in direction to that originally present, i.e., the error is slightly overcorrected. If, on the other hand, the shadow moves originally *against* the mirror, the eye has a myopia greater than -1 D; the same procedure as that just described is followed, using concave lenses. Since the point of reversal indicates a myopia of -1 D, 1 diopter must be subtracted in each instance in order to obtain the actual value of the refractive error. In other words, a lens of $+1$ D makes the eye more myopic by -1 D than it actually is. If the total value of the lenses added is only $+1$ D the eye is obviously emmetropic.

BIOMICROSCOPY—THE SLIT LAMP. By means of this instrument an intense narrow beam of light is thrown obliquely into the eye and a small section of the cornea, anterior chamber, iris, lens or anterior part of the vitreous observed stereoscopically through a binocular microscope. The beam passes through an adjustable slit which when narrowed to minimum width concentrates the beam of light upon an area as small as 0.05 mm. in diameter. The illuminated section is in the form of a prism, or more correctly of a parallelepiped. The tissues within this section are magnified some 25 diameters. Under this method of examination ocular structures which ordinarily appear homogeneous show a definite pattern, and any abnormality is readily recognized by one familiar with the appearance in health. For example, the anterior and posterior epithelial layers of the cornea are seen as bright lines bounding the less luminous substantia propria, and any pathological condition, e.g., erosions, small opacities, keratitis, etc., are easily detected. The laminated structure of the lens is clearly revealed. The central nucleus and the cortical layers are marked by luminous boundaries; the lens sutures appear as darker lines.

ENTOPTIC PHENOMENA. Visual sensations may arise from images of objects situated within the eye itself. The most familiar of these are the

muscae volitantes (L. *flying flies*) which are seen as faint specks projected a short distance in front of the eye. They are due to shadows cast upon the retina by small semi-opaque particles in the vitreous body, such as epithelial cells, small coagula or embryonic rudiments. Particles lying close to the retina are most likely to give rise to the sensations. Lying behind the axis of rotation of the globe such particles cast shadows which move downwards over the retina when the eye is turned upwards but, since the direction of any movement on the retina is reversed in consciousness, they appear to move upwards. This upward movement is followed by a slower downward movement. When any attempt is made to fix one's sight upon the specks they dart away, from which fact the name was probably derived. The movements of shadows caused by particles in the anterior chamber or in any part of the eye in front of its axis of rotation would, of course, be in the reverse direction.

Ordinarily the retinal vessels which, it will be recalled, lie outside the fovea and superficial to the retinal layers, are not perceived. One probable reason for this is that we have come through habit to ignore them, but other factors of a more physiological or anatomical nature have been suggested. Helmholtz, for example, thought that the sensitivity of the retina underlying the vessels was greater than elsewhere, so that the light reaching the retina through them, though reduced in intensity, caused as great an effect as light falling in unshielded regions. At any rate, when light is thrown into the eye at such an angle (e.g., obliquely through the sclerotic) that the shadows of the vessels fall upon a retinal region unaccustomed to receive them, they become visible. If, while his eye is being illuminated in this way in a dark room, the subject looks towards a screen he sees a highly magnified image projected against the uniform surface. The vessels appear as an intricate branching pattern against a bright ground and are known after their discoverer, as *Purkinje figures*. A method which anyone can employ by himself to make the extrafoveal capillaries visible is to look at a bright surface through a pin-hole in a card held close to the eye while he oscillates the opening quickly from side to side and thereby shifts the shadows from point to point in the retina. The capillaries may also be observed by looking through a microscope from which the objective (but not the eyepiece) has been removed and moving the head rapidly from side to side.

Mueller (1855) made use of Purkinje's observation (1811) to prove that the light sensitive elements are the rods and cones. Moving the source of light causes the images to change their positions on the screen. If we measure the distance of this shift (fig. 446, A-B) and the distance between the two positions of the light (a-b) then, knowing the distance of the nodal point of the schematic eye (N) from the retina and from the screen, the position of the shadow (α - β) relative to the vessels (v), i.e., the distance α v, can be calculated. This was found to be from 0.17 to 0.36 mm., which is by actual measurement the approximate distance of the vessels in front of the rod and cone layer.

The corpuscles moving in the retinal capillaries can be observed if the eye is directed to a uniformly illuminated surface. The best way to perform this experiment is to look at the sky through a dense blue-violet glass plate. The blood cells then appear projected upon the plate. It is actually possible to calculate the speed of the corpuscles from the distance between their positions at the beginning and end of a given time interval. Vierordt (1873) was the first to make such an estimation. Knowing the distance of the nodal point of the eye from the retina and from the glass screen, the magni-

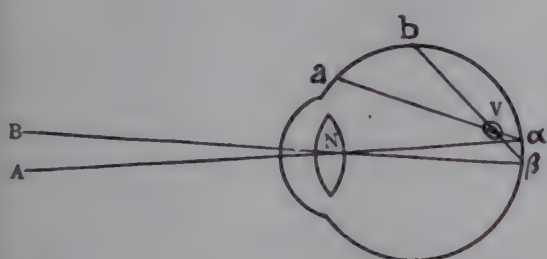


FIG. 446. Description in text.

fication of the travelled distance can be determined (p. 988).

Other entoptic phenomena which should be briefly mentioned are the colored halos seen around bright lights, especially in dark surroundings. The halos consist of a series of concentric rings of rainbow colors—from blue to red from within out. Actually they are diffraction spectra, due to the structures of the eye acting as diffraction gratings. There are two kinds of halo—*lenticular* and *corneal*. The first is attributed to the radial fibers of the lens and is the larger. The corneal type is believed to be due to the epithelial and endothelial cell layers of the cornea.

THE ACCOMMODATION OF THE EYE

ANATOMICAL SKETCH

Before giving an account of the physiological mechanism of accommodation, the structures concerned, e.g., the ciliary body and the crystalline lens will be briefly described.

THE CILIARY BODY. When the interior of the anterior half of the eyeball is exposed by a transection through its equator, a transparent disc—the *crystalline*

lens—is seen occupying the center of the bowl-shaped structure (fig. 447). On the wall of the globe some distance behind the circumference of the lens lies the dendate border of the retina proper known as the *ora serrata* (p. 956). The ciliary body is a circular zone of tissue extending forwards from the ora serrata to a short distance from the circumference of the lens. It is covered on its inner aspect by the pigment layer of the retina, which we have seen is continued forwards (as the *pars ciliaris retinae*) from the point of termination of the neural layers. The ciliary body consists of three parts, the orbiculus ciliaris, the ciliary processes and the ciliary muscle. The *orbiculus ciliaris* immediately adjoins the choroid, of which it may be considered the direct continuation. It is a band about 4 mm. broad encircling the eyeball and presents on its inner aspect a number of radially arranged ridges. The *ciliary processes* appear as some seventy triangular elevations on the inner aspect of the ciliary body; they project towards the axis of the eye and form a series (*corona ciliaris*) of radial fringes which completely

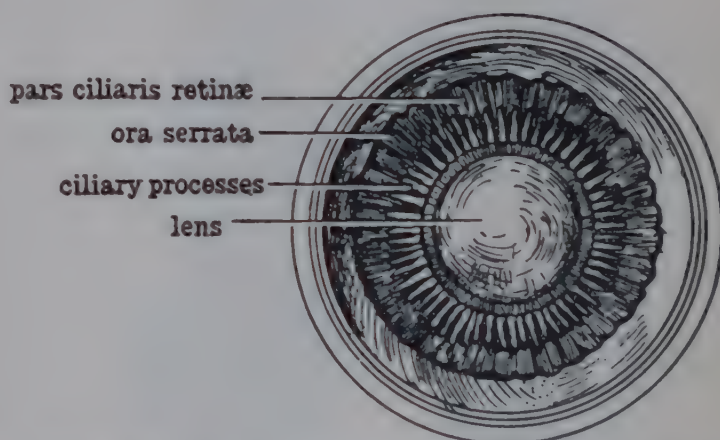


FIG. 447. Showing interior of anterior half of the eyeball.

encircle the equator of the lens, but are separated from it by a very short interval. The great bulk of the ciliary body is composed of the ciliary processes and the ciliary muscle. The fibers of the *ciliary muscle* are arranged in two sets, an outer *meridional* and an inner *circular*. The meridional fibers arise from the scleral spur (p. 1004); radiating backwards and laterally they are attached to the ciliary processes and to the orbiculus, and through the latter to the choroid. The circular fibers are fewer; in meridional sections of the globe they appear as a small bundle of cross-sectioned fibers lying behind the angle of the iris (fig. 448). As a matter of fact, these fibers are not uniformly circular in direction but take different courses and, interlacing with one another, form a reticulated ring-shaped band (fig. 449). Taken as a whole this part of the ciliary muscle constitutes a sphincter (*sphincter muscle of Mueller*) situated in front and to the outer side of the ciliary processes. The fibers composing the margin of the central opening are mainly circular and are attached to a band of elastic tissue situated at the angle of the

iris; the outer circumference of the sphincter is connected to elastic fibers which are continuous with similar fibers of the choroid. The muscle is thus anchored by two elastic attachments.

THE CRYSTALLINE LENS is a transparent, biconvex, circular structure about 11 mm. in diameter and between 3.6 and 3.9 mm. thick at the center. It is situated with the center of its anterior surface coinciding with the center of the pupil; the pupillary margin lies in contact with this surface. The center of the anterior surface is termed the *anterior pole* of the lens, the center of its posterior surface, the *posterior pole*. An imaginary line joining the poles is called the *principal axis*. The two surfaces meet at the circumference in a rounded edge termed the *equator*. The posterior surface in the young adult is decidedly more convex than the anterior

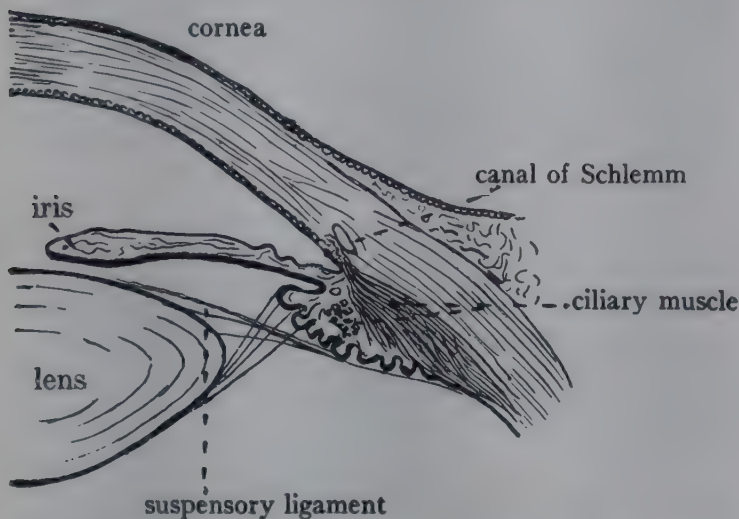


FIG. 448. Showing structures in the region of the angle of the iris.



FIG. 449. Showing arrangement of circular fibers of the ciliary muscle. (After Fincham.)

(see table, p. 986); this difference diminishes somewhat with age. The lens is enclosed in a structureless, highly elastic capsule. The latter is not of uniform thickness, being thinner over the posterior than over the anterior surface, and the part covering the central region of each surface is thinner than the corresponding peripheral parts. The values in ascending order of thicknesses are, center of posterior surface (av. 2.2μ), peripheral part of posterior surface (av. 13.7μ), center of anterior surface (av. 15.7μ), peripheral part of anterior surface (av. 18.2μ) (see fig. 450). A single layer of columnar epithelial cells covers the anterior surface of the lens immediately beneath the homogeneous capsule; the latter is formed as a secretion of these cells. The substance of the lens consists of a series of ribbon-like fibers which arise from the region of the equator and

are actually greatly elongated epithelial cells (fig. 451). By careful examination of the lens, from the most central part of the anterior surface to the region near the equator the gradual transition of the columnar cells into the attenuated cells of the lens substance can be traced. The fibers proceed from the equator toward the lens center and, abutting against fibers coming from other segments of the periphery, fuse along well-defined lines—the *lens sutures*. These are seen in the adult lens as a series of faint irregular striae radiating from the center to form what is known as the *lens star*. On section, the lens shows a series of concentric lamellae with a nucleus of extreme convexity and high refractive index, and a less refractive cortex. The optical advantages of this construction have been pointed out (p. 986). The nucleus is also of much firmer consistency than the cortex which is relatively soft and pliable.

The interval between the ciliary processes and the equator of the lens is occupied by a circular membrane



FIG. 450. Showing the regional variations in thickness of the lens capsule. (After Fincham.)

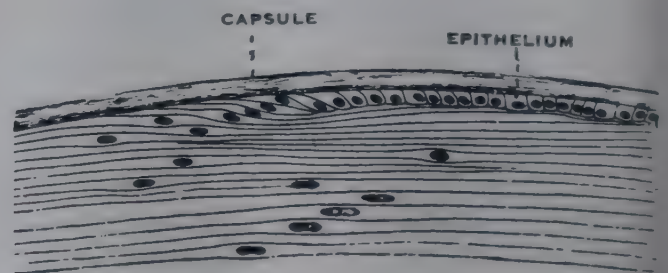


FIG. 451. Meridional section of the lens. (From Wolff after Poirier and Becker.)

band; this is the anterior part of the *zonula ciliaris* (*zonula of Zinn*). The precise origin of the fibers of the zonula is disputed, but they appear to arise as a system of transparent fibers from the anterior part of the hyaloid membrane (p. 1002) 1.5 mm. or so in front of the ora serrata. Passing forwards they form a series of bundles which occupy grooves between the ciliary processes, and then bridge the gap, as just mentioned, between the ciliary processes and the lens. Near the lens circumference the zonula splits into an anterior and a posterior lamina; the former is the thicker of the two and blends with the lens capsule a little in front of the equator, constituting what is generally known as the *suspensory ligament* of the lens. The space between the two layers of the zonula is called the *canal of Petit*. Slits in the layers of the membrane establish communications between the canal of Petit and the anterior chamber and the region behind the lens (post-lenticular space, p. 1002).

THE MECHANISM OF ACCOMMODATION

Light rays from an object at infinity, which is taken as any point more than 20 feet distant, are parallel and are brought to a focus (principal focus) on the retina of the emmetropic eye. Rays from a near object are divergent, but they too are brought to a sharp focus. This adjustment of the dioptrics of the eye whereby it is able to focus the image of both far and near objects is called *accommodation*. That the refracting power of the eye does actually undergo a change when it is turned from a far to a near object or vice versa was shown by Scheiner (1619) by a simple experiment. A card with two pin-holes separated by a



FIG. 452. Illustrating Scheiner's experiment. o represents position of needle; ee, pinholes in card; RR, screen with image of needle focussed at I. When the screen is moved forward or backward ($R'R'$ or $R''R''$) two images ($e'f'$ and $f''e''$) appear. In the case of the eye, a double image of the needle is seen if the sight is accommodated for a farther or nearer object. The image of the needle is focussed behind the retina (represented by $R'R'$) in the first instance, and in front of the retina (represented by $R''R''$) in the second.



FIG. 453. Purkinje-Sanson images. A, during far vision; B, during accommodation for near vision. (Redrawn and modified from Williams.)

distance less than the diameter of the pupil is held before one eye. The eye is focussed upon a needle held in front of the card and perpendicular to a line joining the two holes. The needle appears single; but it appears double if the eye is focussed upon an object placed either beyond it or between it and the eye. The explanation will be evident from fig. 452.

There are at least three possible means by which accommodation of the eye could be brought about. The retina might be moved towards or away from the lens, i.e., the eye might be elongated or shortened so that divergent rays in the one instance or parallel rays in the other would be accurately

focussed. This mechanism is actually made use of in the mollusc pecten. That it is not the method followed by the human eye was disproved by Young (1801). A second possibility is that the distance between the retina and the lens is altered by a movement of the lens; this is the method used in photography, the distance between the film and the lens can be nicely adjusted for the focus of near objects. In the bony fishes accommodation is effected in such a manner.⁴

Variations in the convexity of the crystalline lens and consequently of the converging power is the third alternative. This is the method first suggested by Young for the human eye; the conception was later elaborated by Helmholtz. That

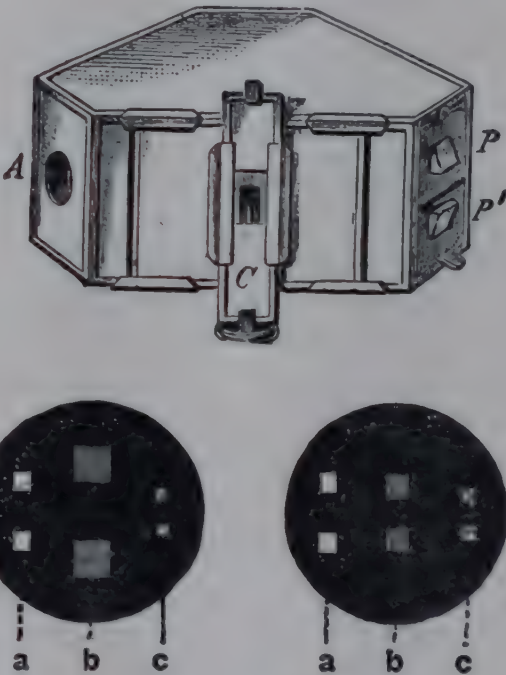


FIG. 454. The phakoscope. Description in text (footnote 5). (After Helmholtz.) Reflections from cornea (a), anterior surface of the lens (b) and posterior surface of the lens (c) during far (left) and near vision (right).

such is the mechanism adopted by mammals in general is now almost universally accepted. A change in the convexity of the anterior surface of the lens during accommodation is a well-established fact and one which can be demonstrated by

⁴ These fish are myopic when the eye is at rest, i.e., the eye is adjusted for near vision; accommodation for far vision is an active process consisting of contraction of a structure called the campanula which moves the lens backward. In some birds the central part of the anterior surface of the lens moves forwards into the pupillary aperture and as a result of pressure against the rigid margin of the iris becomes highly convex. In other avian species the cornea consists of two lamellae, the posterior being drawn backwards during accommodation for far vision. In others again (owls and hawks) the curvature of the cornea is increased during near vision.

the following experiments. A lighted candle is held to the outer side and a little in front of the eye of a subject in a darkened room. Three images (Purkinje-Sanson images fig. 453), within the subject's pupil, will be seen by an observer, one bright and erect reflected from the cornea, another larger, erect and less well-defined from the anterior surface (epithelial layer) of the lens which like the cornea, acts as a convex mirror. The third image is inverted, dim and smaller than the other two; it is reflected from the posterior (concave) surface of the lens. The subject is directed to gaze into the distance while the positions of the images are noted; he then looks at a near object when a change in the size and position of the reflection from the anterior surface of the lens will be observed. It becomes smaller and moves towards the corneal image which, of course, remains stationary. This must mean that the anterior surface of the lens has become more convex. The third (inverted) image shows little change in size or position.⁵ Now, if one knows the radius of curvature of the cornea, which can be measured by means of an instrument known as an ophthalmometer, then the radius of curvature of the surfaces of the lens and the changes in their curvature during accommodation can be calculated from careful comparative measurements of the sizes of the images from the cornea and lens. The average values for the radius of the anterior surface of the lens in five subjects examined by Fincham were 12.2 mm. for the "resting eye" and 6.8 mm. during accommodation for near vision. The change in curvature of the posterior lens surface was slight (about 0.5 mm.). The average increase in thickness of the central part of the lens was 0.47 mm., while the equatorial diameter diminished by 0.5 mm. The center of the anterior surface moved forward by from 0.3 to 0.4 mm. In general terms the change in shape of the lens during accommodation for near

vision can be summed up as follows. The central part of the anterior surface becomes more convex; the posterior surface shows little change. The peripheral region of the anterior surface actually becomes somewhat flatter, this surface taken as a whole therefore assumes a hyperbolic form.

The manner in which the change in shape of the anterior surface of the lens is brought about was explained by Helmholtz as follows. When the eye is accommodated for distant vision the suspensory ligament which, as we have seen, is attached to the lens capsule, is drawn taut as a result of the pull of the elastic structures, e.g., the ciliary body and choroid. The peripherally directed traction exerted upon the lens capsule through the suspensory ligament results in flattening of the curvature of the anterior surface of the lens. Focussing the image of a near object is accomplished by contrac-

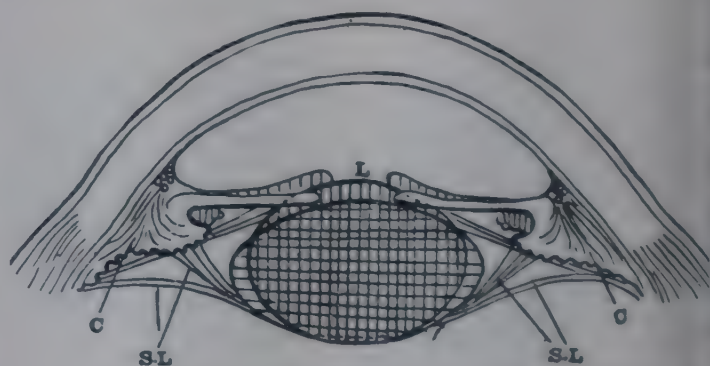


FIG. 455. Illustrating the mechanism of accommodation of the eye for near vision. The horizontally shaded lens and the unshaded iris show the position of the parts when at rest; the vertically shaded lens and iris show the position during accommodation for a near point. C, ciliary muscle; S.L., suspensory ligament (Redrawn from Landolt.)

tion of the ciliary muscle which, by drawing the choroid forward, permits the ciliary processes to move forward and inward, thus reducing the diameter of the ring (corona ciliaris) which they form. The suspensory ligament and lens capsule are thus relaxed, and the lens, by virtue of its inherent elasticity, assumes a more convex form (fig. 455). The excised lens, i.e., one released from the restraint of surrounding structures, is therefore at its maximum convexity. Helmholtz's conception is supported in its main tenets by modern work. The movement inward of the ciliary processes during accommodation for near vision has been observed in the living human eye; and in an eye from which the lens substance had been adsorbed as a result of injury, tightening and slackening of the empty capsule was seen during the corresponding phases of accommodation. Yet the curvature assumed by the anterior surface of the

⁵ The *phakoscope*, an instrument invented by Helmholtz, may be employed for observing the images. It consists of a small hexagonal dark box (fig. 454) with an aperture (A) for the examiner's eye and another for the eye of the subject. A candle placed in front of the prisms, P and P' throws a pair of images (squares of light) upon each of the three reflecting surfaces of the observed eye. The aperture for the subject's eye is in the side of the box opposite to the window C. While his eye is being observed the subject gazes into the distance and then accommodates for near vision by fixating a needle placed in front of the window. This method of observation has the advantage that it is easier to detect a change in the distance between a pair of squares (which, of course, will indicate a corresponding change in size of the double image) than a change in size of a single image such as that of a candle flame.

lens is, as mentioned above, *hyperbolic*, whereas one would expect it to assume a spheroid form were the lens substance itself elastic and the change in shape due simply to its recoil when released from restraint.

The details of the mechanism with respect to this point have been elucidated by the work of Fincham. According to this observer, the change in shape of the lens during accommodation is explained by the high elasticity of the lens capsule and of the regional variations in its thickness (p. 994), together with the pliable nature of the cortical part of the lens as compared with the nucleus. When the lens is accommodated for distant vision, its substance is confined under tension within the capsule and, as a consequence, distends the latter to the greatest degree where it is weakest, (i.e., thinnest) namely, on the posterior

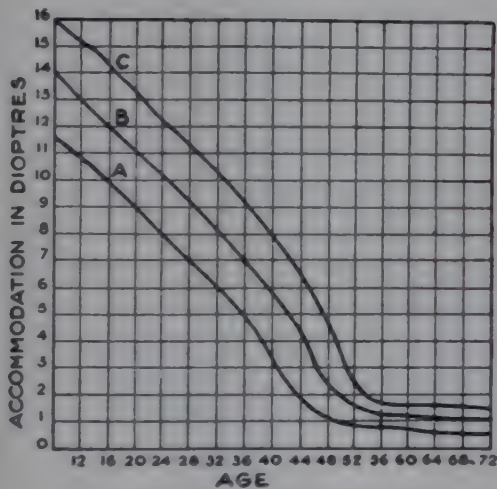


FIG. 456. The amplitude of accommodation at different ages. A. The lowest physiological values. B. Average values. C. Maximum values. (After Duane.)

surface. The convexity of this surface is therefore near its maximum when the eye is adjusted for distant objects and little further change can occur during accommodation for near vision. Upon contraction of the ciliary muscle and the consequent slackening of the suspensory ligament the recoil of the elastic capsule moulds the plastic cortex; the peripheral part of the anterior surface is thus pressed back by the relatively thick capsule but the thinner central part of the latter permits the lens substance, chiefly the highly convex nucleus, to bulge forwards.

THE VISUAL AXES AND PUPILLARY DIAMETER DURING ACCOMMODATION. The complete act of accommodation for a near object comprises, besides an increase in the convexity of the lens, *convergence of the eyes* and *constriction of the pupil*. The constriction of the pupil which occurs during accommodation serves two purposes. The nar-

rowed aperture of the iris reduces chromatic and spherical aberration (p. 999), thus increasing visual acuity, and diminishes the quantity of light (which is relatively greater from near objects) entering the eye.

The range and amplitude of accommodation. The farthest point from the eye at which an object can be seen clearly is called the *far point* or *punctum remotum*. The corresponding point nearest the eye is termed the *near point* or *punctum proximum*. In the emmetropic eye the far point is at infinity, i.e., at a distance of over 20 feet (6 meters) and the near point at from 7 cm. to 40 cm., depending upon age (fig. 456). The difference between the far and the near point distances is termed the *range of accommodation*. The difference between the refracting power of the eye when accommodation is completely relaxed for the far point and fully displaced for the near point is called the *amplitude of accommodation*. The far point is conjugate to a point on the retina, i.e., parallel rays entering the eye come to a focus on the retina and rays from the latter upon emerging from the eye are parallel and would meet at infinity. In the accommodated eye the near point is conjugate with a point on the retina. The focal length of the eye in each state of accommodation therefore corresponds, respectively, to the far and near point distances. It will be recalled that the refractive power is expressed as the reciprocal of the focal distance, the unit being 1 meter and called a diopter. The reciprocal of the far point distance is termed the *static refraction* (designated R) of the eye, and that of the near point distance, the *dynamic refraction* (P). The difference between the two (P-R) gives in diopters the amplitude of accommodation. In the emmetropic eye, since the far point is at infinity, the static refraction is taken as zero. When the near point is at 10 cm. the dynamic refraction is $\frac{100 (1 \text{ meter})}{10} = 10 \text{ D}$. The amplitude of accommodation in such an emmetropic eye is therefore 10 D.

The amplitude of accommodation diminishes progressively from childhood to about sixty years of age being 16 D at twelve years, 6.5 D at the age of thirty and only about 1 D at sixty. In other words, with advancing years the near point gradually recedes from the eye and at sixty years of age an object must be 1 meter distant in order to be clearly focussed upon the retina (see *presbyopia*, p. 1000). This phenomenon is due in the majority of instances to physical changes in the properties of the lens and its capsule (reduced plasticity of the one or diminished elasticity of the other); it occasionally results from weakness of the ciliary muscle.

THE METABOLISM AND COMPOSITION OF THE LENS. The lens is entirely epithelial in structure and devoid of blood vessels; it receives its nourishment from the fluids bathing its surfaces, e.g., the aqueous humor and

the fluid of the vitreous. The capsule acts as a semi-permeable membrane which separates substances of high osmotic pressure (equiv. 1.2% NaCl) within the lens from the osmotically less active aqueous. During accommodation, when the pressure within the lens is around that of the general intraocular pressure, fluid presumably would as a result of this higher osmotic pressure pass inwards across the capsule; on the other hand, when the ciliary muscle is relaxed as a reverse movement of fluid is to be expected, for the tension exerted upon the capsule will, by raising the intra-lenticular pressure reverse the pressure relationships and drive fluid out.

As one might expect the metabolism of the lens is low; Adams has demonstrated a small but definite oxygen uptake (30 cu. mm. per gram of lens per hour). An autoxidation system has been shown by Goldschmidt and by Adams; this consists of (1) *glutathione* which is in high concentration in the lens as compared with other tissues and (2) a *thermostable protein residue* identified as β -crystalline. These two are maintained in chemical equilibrium by an oxidation-reduction of the SH \rightarrow SS type. Though other tissues possess such an autoxidative system, in them it plays a secondary rôle, whereas in the respiration of the lens it is believed to be of paramount importance.

Four types of protein have been identified in the lens substance, (a) a *euglobin* or "*albuminoid*" (17%) which is water-soluble, and two water-soluble proteins—*pseudoglobulins*, (b) α -crystalline (11%) and (c) β -crystalline (6%), together with (d) a small quantity of albumin (0.2%). The albuminoid is present mainly in the nucleus, α -crystalline chiefly in the superficial part of the cortex and β -crystalline in the deeper parts. The two crystallines are particularly rich in the sulphur-containing amino-acids cystine and cysteine. The lens proteins as first shown by Uhlenhuth are *organ specific* not species specific, thus differing in their immunological behaviour from red cells (p. 49) and blood serum. For example, a solution of lens protein when injected into an animal of the same or of another species causes the production of an antibody—a *precipitin*. This anti-serum has then the power to precipitate a solution of lens protein from wherever derived, i.e., from a species other than the one which supplied the anti-serum, from the same species or even from the same animal.

The lens substance contains a high concentration of potassium—400 mgm. per 100 grams of wet weight—as compared with about 3 mgm. per cent in the aqueous and 20 mgm. per cent in serum. The concentrations of calcium (5 mgm. per cent), sodium chloride (300 mgm. per cent) magnesium and silicates are relatively low. The total salt concentration is between 0.7 and 0.8 per cent. Cholesterol and phosphatides amount to about 200 mgm. per cent in young lenses, but are from two to four times this value in older specimens.

CHANGES IN THE LENS WITH AGE—CATARACT. The loss of plasticity and elasticity of the lens with age as a result of a gradual sclerosis, and the

effect such changes have on the mechanism of accommodation are referred to on p. 999. Some alterations in lenticular color may accompany the sclerosing process; amber tinting, or even a reddish or brownish discoloration of the lens with consequent filtering of the shorter rays, is of common occurrence.

Cataract is the name given to any partial or complete opacity of the lens. In the commonest variety no ocular or general disease which can be held responsible precedes the development of the opacity, and this, since it appears to be simply a manifestation of age, is termed *senile cataract*. The process leading to the opacity is degenerative in nature, not inflammatory for the lens is, as just stated, avascular. The opacity commences usually in the deeper part of the cortex and does not, as a rule, involve the nucleus. The lens swells as a result of accumulation of fluid between the fibers, the anterior chamber becoming shallow. So long as the superficial layers of the cortex are clear the cataract is called *immature*. It is said to be *mature* when the opacity has extended to include the superficial layers.⁶ The water content of the lens has by this time returned to normal. The mature stage is followed by disintegration of the cortex which becomes softened into a pulsataceous mass; this is the stage of hypermaturity; drying and shrinkage of the lens finally result.

The essential change in the cataractous lens is a progressive coagulation of the lens proteins. According to the most generally accepted explanation, such a process is due to the prolonged action of ultraviolet light, and, in some instances, to the thermal effect of infra-red rays. The lens as already pointed out (p. 960), by absorbing a large proportion of the rays between λ 400 m μ and 300 m μ protects the retina from their injurious effects. Wave lengths below 297 m μ are absorbed by the cornea. The rays absorbed by the lens are not without their effect upon the lens substance itself; it is these which cause the physical change in the lens proteins. Two stages are recognized in the coagulation process, (1) *denaturation of the lens proteins*, consisting presumably of a molecular rearrangement, by light or heat which renders them susceptible to (2) *aggregation (agglutination) of the protein particles* into a flocculent mass—coagulation. This ultimate result occurs only in the presence of certain salts and is enhanced by some organic substances, e.g. dextrose and acetone. The theory that radiant energy is responsible for denaturation of the lens proteins is in accord with many observations. For example, the absorption by the lens of the shorter rays increases with age. The

⁶ As long as a clear interval exists between the opacity and the iris (which lies in contact with the anterior surface of the lens) the latter throws a shadow upon the former. When the opacity involves the entire thickness of the cortex, i.e., right up to the iris, there is no shadow.

opacity commences in the lower quadrant of the lens which receives the most intense light. In tropical countries, e.g. India and Egypt, cataract is much commoner than in temperate latitudes; it is also less frequent in the latter than in Arctic zones, presumably as a result of the high content in acitinic rays of the light reflected from snow and ice. It is also stated that on this continent the incidence of cataract increases from temperate zones to the equator, and that it is also higher in those who work in the fields than in city dwellers. Burge's experiments and the more recent ones of Clarke show convincingly the effect of light upon the development of lenticular opacities. Burge found that whereas exposure of a solution of lens protein to ultraviolet light for 100 hrs. did not cause coagulation, this occurred if CaCl_2 , MgCl_2 , dextrose or acetone were added. Moreover the exposure of the eye of a living fish or frog to short light waves was without effect if the animal had previously been kept in tap water, but definite opacity of the lens followed a few hours exposure, if the fish or frog had been for some days in water containing 0.8% calcium chloride, 0.1% dextrose or 0.1% sodium silicate. Clarke found that heat enhanced the action of the light rays upon solutions of lens proteins, and that opacity could not be produced in the absence of calcium.

The incidence of cataract is much higher in diabetics than in normal persons; it is usually of the ordinary or so-called senile type, but it occurs at an earlier age. The opacity is attributed to the action of dextrose and possibly of acetone bodies in rendering the lens proteins more readily coagulable by light. Duke-Elder believes that as a result of the high blood sugar, the osmotic relationships between the lens and the surrounding fluids are disturbed and the nutrition of the lens thereby interfered with.

Though the factors outlined above appear to be the main ones concerned in the production of the common or senile type of cataract, opinions differ considerably as to the details of the mechanism involved, as well as in regard to the production of other types of lenticular opacity. It is suggested, for example, that the action of ultraviolet rays in inducing denaturation of the lens proteins is due to the reduction of the glutathione and β -crystalline content and the consequent depression of the autoxidative mechanism. Such an effect of ultraviolet radiation has been shown experimentally; it has also been established that the content of the lens in glutathione and in the thermostable protein residue diminishes with age. The power of the lens to fluoresce upon exposure to short wave radiations (p. 960) and the disposal of the surplus energy by converting them into long waves, is considered by Burge to be an important factor in ameliorating the effect of light upon the lens; fluorescing bacteria for example are much less readily killed by ultraviolet light than are other types. It is of some considerable interest therefore that the power of the lens to fluoresce diminishes with age. In glass blowers' cataract, infra-red rays would

appear to play an important auxiliary rôle. Hartridge and Hill believe that these act indirectly by increasing the production of aqueous humor by the ciliary processes and iris which leads to disturbances in the fluid interchanges between the lens and its surroundings, the nutrition of the lens suffering as a result. They point out that the lens absorbs only about 12% of the heat rays which enter the eye whereas the iris absorbs all which reach it; it is unlikely, therefore, that their action upon the lens proteins is direct. Heat rays may act, however, simply by accelerating the denaturing action of ultraviolet light (Clarke). Duke-Elder, on the other hand, suggests that the heat rays affect the permeability of the capsule, with consequent upset in the osmotic relationship between the lens substance and the aqueous.

An interesting type of cataract is that following parathyroidectomy; disordered calcium metabolism would appear to be in some way concerned in its production; the calcium content of the lens is increased, whereas that of the blood is reduced. There is no definite evidence, however, to connect ordinary senile cataract with parathyroid deficiency, but there seems little doubt that calcium is concerned in some obscure way with cataract development. A favorite method of producing cataract for experimental study is by the injection of naphthaline; opacities form only if the animal is on a low calcium diet. In rats, lenticular opacity is readily produced by a diet containing a high percentage of lactose or galactose; the former sugar increases the absorption of calcium, but whether this fact has any bearing upon the development of the cataract is difficult to say; it does not dovetail with other observations in respect to calcium and the development of cataract.

The composition of the cataractous lens shows marked differences from the normal. There is an increase in the insoluble albuminoid and a decrease of the soluble proteins and of glutathione; the oxygen uptake is much reduced. Of the inorganic constituents calcium shows a relatively enormous increase (up to 140 mgm. per cent). The concentration of magnesium, sodium and silicates is also raised, whereas that of potassium is greatly reduced.

OPTICAL DEFECTS

SPHERICAL ABERRATION. Rays traversing the peripheral parts of an ordinary convex lens are refracted more strongly and therefore come to a focus nearer the lens than do those transmitted through more central regions. In other words, the outer and inner rays cross in front of the retina and a blurred image is formed (fig. 457). This is an inherent defect of convex lenses and is called *spherical aberration*; in the manufacture of a camera lens, special means are employed to correct it, the lens being built up of separate pieces of glass of different refractive indices cemented together so that all rays are converged to the same point.

Spherical aberration is corrected in a somewhat similar manner in the crystalline lens, the nucleus having a higher refractive power than the periphery (see p. 986). The iris, since it covers the outer part of the lens and shuts off the peripheral rays, also serves to correct this defect.

CHROMATIC ABERRATION. The colors composing white light are refracted to different degrees according to their wave lengths. The violet rays are refracted most, the refractibility diminishing progressively from the violet to the red end of the spectrum (fig. 458). For this reason a series of fringes, colored from violet to red from within outwards, borders the image formed by a simple cheap lens. *Chromatic aberration*, as this defect is called, is corrected in camera and microscope lenses by cementing a biconvex lens of crown glass to a

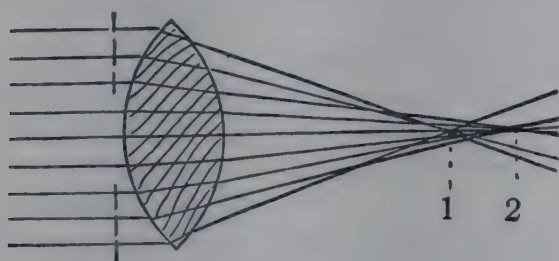


FIG. 457. Spherical aberration. Outer rays meet at 1, inner rays at 2.

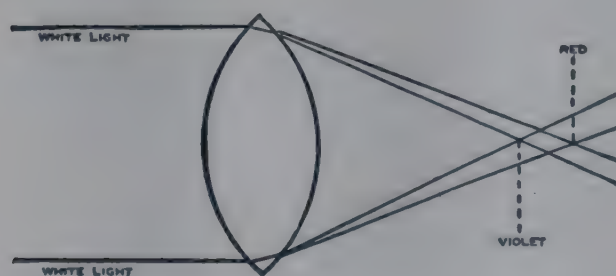


FIG. 458. Chromatic aberration.

concave one of flint glass. Such a lens is called *achromatic*. The lens of the eye is only partially corrected for chromatic aberration (p. 986). A red and a violet object at the same distance from the eye therefore cannot both be seen sharply at the same time. If, for example, the eyes are focussed upon a violet light, they must accommodate, in order to maintain the focus, when the light is changed to red. In ordinary vision the colors surrounding the images on the retina are not perceived; we have come to ignore them.

Diffraction and the scattering of light within the eyeball. Light is diffracted by the pupillary margin and by the lens fibers and corneal epithelium; as a result of this and of spherical aberration the retinal image is not made up of points of light but of diffusion circles (blur circles),

i.e., a bright central disc surrounded by light rings which diminish in intensity by almost imperceptible gradations towards the periphery. The relative size of the central bright area varies inversely with the diameter of the pupil and directly with the wave length of the light. The opposite effects of changes in the size of the pupil upon this defect and upon chromatic aberration have been pointed out (p. 983).

None of the ocular media is perfectly homogeneous; owing to their colloidal nature a certain proportion of the light entering the eye is scattered (Tyndall phenomenon), that is, it is not focussed upon the retina but is deflected from the course which it would follow according to the laws of refraction if the contents of the globe were perfectly transparent. The colloidal particles have a size of the order of the wave length of light. The quantity of scattered light is directly proportional to the square of the size of the particles, and inversely proportional to the fourth power of the wave length (Rayleigh). Thus the greatest scattering within the eyeball occurs with violet and ultraviolet light and the least with red. The dispersion of ultraviolet rays probably serves a useful purpose in that the retina is thus protected from their injurious effects.

PRESBYOPIA (Gr. *presbos*, old; *ops*, the eye) is the term given to the gradual reduction in the amplitude of accommodation which goes hand in hand with advancing years.

EMMETROPIA AND AMETROPIA. The four optical defects just described may be regarded as physiological, the first three being inherent to some extent in optical systems in general; the fourth is a natural accompaniment of age. Two other defects of frequent occurrence are due to incongruity between the length of the eyeball and its refracting power and must be classed as definite abnormalities.

The refractive state of the normal eye, which has its far point (p. 997) at infinity, i.e., at a distance greater than 6 meters (20 feet), is called *emmetropia*. Parallel rays entering the emmetropic eye are brought to a clear focus on the retina without any effort of accommodation. The static refraction (p. 997) of such an eye is therefore zero. If the far point is not at infinity the eye is *ametropic*. There are two forms of ametropia—myopia and hypermetropia (fig. 459).

In *myopia* (Gr. *myo*, I blink or half close the eye; *ops*, the eye) or *short sight*, the eyeball is too long relatively to its refracting power (fig. 459, B). Obviously, such an eye will bring parallel rays to a focus in front of the retina, i.e., in the vitreous. After meeting, the rays cross and form a blurred image or a diffusion circle upon the retina, just as a camera which is extended too far forms an indus-

tinct image upon the film. In order to form a clear image on the retina of the myopic eye the rays must be, not parallel but divergent; such as are emitted by a near object. The far point is therefore at a finite distance, and in extreme instances may be only a few centimeters from the eye. Accommodation, of course, is relaxed for the far point as in the emmetropic eye for, obviously, increasing the converging power of the lens will only cause greater blurring of the image. The far and near points being close together, the range and the amplitude of accommodation (p. 997) are reduced. Myopia is corrected by means of concave (diverging) lenses. If, for example, an object can be seen clearly no farther away than 1 meter, the myopia is -1 D, i.e., a concave lens of this power is required.

In *hypermetropia* (Gr. *hyper*, above; *metros*, measure; *ops*, the eye) or *long sight* (fig. 68C) the eye is too short for its refracting power.⁷ There-

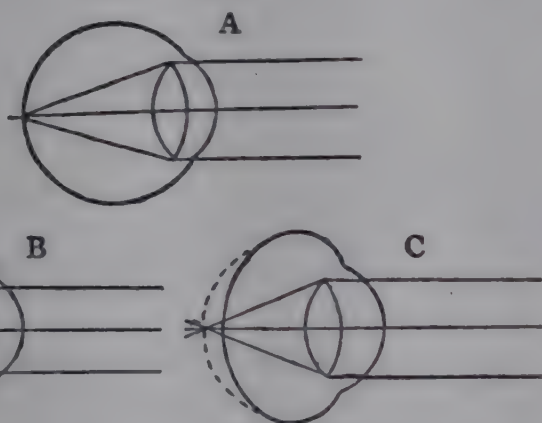


FIG. 459. A, emmetropia; B, myopia; C, hypermetropia.

fore parallel rays after refraction fall upon the retina before they have come to a focus, and form an image blurred by diffusion circles. The far point lies, as it were, "beyond infinity" and is *virtual*, i.e., it is behind the eye at the point where the rays would meet if continued backwards through the retina. The hypermetrope must accommodate when he views distant objects in order to focus the parallel rays upon the retina. The range of his accommodation (p. 997) is the same as that of the emmetrope but the amplitude is greater. Suppose, for example, that the near point is 0.10 meter in front of the eye and the far point is 0.25 meter behind, i.e., negative (-0.25).

Then the dynamic refraction is $\frac{100}{10} = 10$ D, and

⁷ Both types of ametropia in the great majority of instances are due to an abnormality in the length of the eyeball and not to any change in the refracting power of the eye.

the static refraction is $\frac{-100}{-25} = -4$ D; the amplitude of accommodation is therefore 10 D $- (-4$ D), or 10 D $+ 4$ D = 14 D. Hypermetropia is corrected by means of a convex lens, the distance of the far point behind the eye giving the measure of the strength of lens required; if this is -0.25 meter then a $+4$ D lens would correct the defect (see p. 991). The larger amplitude of accommodation in hypermetropia is accompanied by hypertrophy of the ciliary muscle; in myopia, on the other hand, the muscle shows atrophy and the circular fibers may be absent.

ASTIGMATISM (Gr. *a*, privative; *stigma*, a point). In this condition, as its name implies, rays of light are not brought to sharp points upon the retina, but form short lines. The defect is present in all eyes to a certain degree, and it is only when pronounced that it can be considered abnormal.

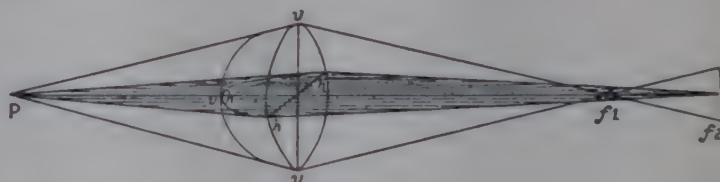


FIG. 460. Showing course of rays in an astigmatic eye. The curvature of the cornea is greater in the vertical meridian *vvv* than in the horizontal meridian *hhh*. Hence the rays of light coming from the point *P* and passing through the vertical meridian come to a focus at *f*¹, while those through the horizontal meridian come to a focus at *f*². (After Waller.)

It must be remembered that rays of light pass through all meridians of a lens; in converging to a focus they therefore form a cone of light, not simply a flat pennant-like beam. If all meridians of a lens have the same curvature, then rays in all planes will be refracted to the same degree and come to a focus together. If, on the other hand, the curvatures differ, the rays transmitted through a meridian with the greater curvature will be refracted more strongly and brought to a focus in front of rays passing through other meridians. For example, should the vertical meridian be more curved than the horizontal, then when the rays passing through the vertical meridian are in focus those in the horizontal will form, not a point, but a horizontal line (see fig. 460). Such inequalities of curvature in the meridians of the cornea or, less commonly, of the crystalline lens, are the cause of astigmatism. The greater curvature may be in either the vertical, horizontal or an oblique meridian. When the subject of astigmatism looks at a clock face, the straight lines in the vertical

numerals XII and VI may be clearly seen, while the horizontal lines in IX and III are blurred, or vice versa. Or, the diagonal numerals may be out of focus while the vertical and horizontal are sharply defined.

Astigmatism is corrected by the use of spectacle lenses convex in the meridian corresponding to that of the cornea (or crystalline lens) having the lesser curvature. Thus if the curvature of the cornea is greater in the vertical meridian, the subject is fitted with a cylindrical lens having its convexity in the horizontal meridian.

THE INTRA-OCULAR FLUIDS

THE INTRA-OCULAR PRESSURE. The pressure within the chambers of the eye of a living animal

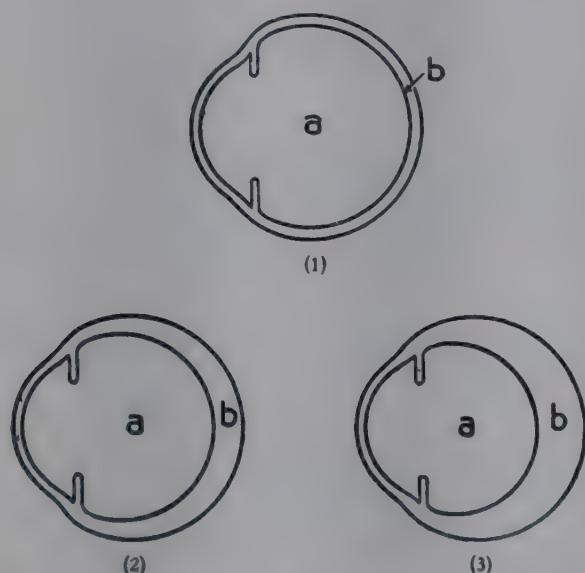


FIG. 461. Showing the distribution of volume-pressure in the eye with (1) a collapsed blood-pressure, (2) in the normal state, and (3) with raised blood pressure and capillary dilatation. (After Duke-Elder. The nature of the intra-ocular fluids.)

is from 20 to 25 mm. Hg and from 8 mm. to 10 mm. Hg in the excised but intact globe; it also falls to the latter level immediately after death or after arrest of the ocular circulation. The difference between these two sets of values, is due to the pressure of the blood in the vessels of the globe. This will be clear from fig. 461. The vascular bed of the eyeball lies between the relatively resistant sclerotic on the outside and the incompressible intra-ocular contents on the other. It is evident that blood pumped into the vessels of the choroid will raise the intra-ocular pressure above that of a bloodless eye. The intra-ocular pressure runs closely parallel with that of the blood in the choroidal capillaries. A rise or fall in general arterial pressure therefore may cause a corresponding change in intra-ocular pressure, though

it will be much less in degree. The pulse beat causes a variation in intra-ocular pressure of from 1 to 2 mm. Hg, and the respiration one of from 3 to 5 mm. Hg. However, since it is the pressure in the capillary bed of the eye rather than that in the larger ocular vessels which is the determining factor and the former pressure can vary as a result of *local* changes in caliber of the minute vessels, the intra-ocular and arterial pressures do not necessarily change in the same direction. Thus arterial hypertension, in which the capillary pressure is not raised (p. 134), does not cause a rise in intra-ocular pressure; amyl nitrite, on the other hand, causes a *fall* in arterial pressure as a result of the peripheral vasodilatation, accompanied by a *rise* in intra-ocular pressure (due to the dilatation of the capillaries of the eye and the consequent increase in capillary pressure). The intra-ocular pressure therefore follows very closely the venous pressure; tying the vortex veins, for example, increases capillary pressure and causes a rise in intra-ocular pressure of from 50 to 60 mm. Hg. The pressure of 8 or 10 mm. Hg which, as mentioned above, exists within an eye immediately after its circulation has been arrested, may be looked upon as representing the balance struck between the production of intra-ocular fluid and its removal through the drainage channels (p. 1003).

Other factors which affect the intra-ocular tension are, pressure from without by the action of the eyelids and of the extrinsic muscles of the eye. The effect exerted by the eye muscles in ordinary movements is negligible, but maximally strong convergence of the eyeballs may raise the pressure by from 4 to 10 mm. Hg. Movements of the lids have a greater influence, strong contraction of the orbicularis oculi causing a rise of 50 mm. Hg or more. Exposure of the eye to light causes a fall, and dark adaptation a rise in pressure which is attributed to constriction and dilatation, respectively, of the ocular capillaries. Contraction of the ciliary muscle causes no change in the intra-ocular pressure, nor does the state of the pupil. A change in pressure does not occur therefore upon accommodation of the eye, provided that the associated convergent movement is prevented.

THE VITREOUS BODY. The vitreous body occupies the segment of the globe lying behind the lens and the ciliary processes. In front it presents a saucer-shaped depression—the *hyaloid fossa*—which lodges the posterior convexity of the lens. A narrow space (*post-lenticular space*) filled with fluid separates the lens from the concave surface of the vitreous. The *hyaloid canal* (which lodged the hyaloid artery in the embryo) runs from the posterior pole of the lens to the center of the optic disc. The structureless *hyaloid membrane* sur-

rounds the vitreous; anteriorly it is strengthened by radial fibers which have already been referred to as the *zonula ciliaris* (p. 994). In this region it shows a series of grooves which lodge the ciliary processes. The vitreous body is a jelly-like material, possessing no obvious structure; but it is claimed that by the use of special fixatives (e.g., a weak solution of chromic acid) a series of superimposed lamellae arranged concentrically around the hyaloid canal and composed of very thin flat cells can be demonstrated. The spaces between the lamellae contain fluid almost identical in composition with the aqueous humor. Though some maintain that the lamellae are fixation artefacts and that the vitreous body is a homogeneous gel, there seems little doubt that a framework does exist. Friedenwald and Stiehler observed it in the vitreous of ox eyes which had been prepared without the use of fixatives. The structural framework contains a protein called *vitrein*. The refractive index of the vitreous is 1.33 (see p. 986).

The AQUEOUS HUMOR is a clear watery fluid occupying the anterior and posterior chambers of the eye. It has a refractive index of 1.33; it is alkaline in reaction (pH 7.1–7.3), has a specific gravity of from 1002 to 1004 and a viscosity of 1.029. Its composition and that of serum are given in the following table, after Duke-Elder.

	Grams per 100 cc. Aqueous humor	Serum
Water	99.6921	93.3238
Solids.....	1.0869	9.5362
Total protein.....	0.0201	7.3692
Albumen.....	0.0123	4.4135
Globulin.....	0.0078	2.955
Fibrinogen.....	—	—
Fats.....	0.004	0.13
Reducing sugar.....	0.0983	0.0910
Non-protein nitrogen.....	0.0236	0.0239
Inorganic constituents Na, K, Ca, Mg, Cl, P and S.....	0.7529	0.7433

The chief differences between the compositions of serum and aqueous are shown in the concentrations of substances of colloidal nature—the proteins and fats. The diffusible non-ionizable substances, such as urea and other non-protein nitrogenous constituents and sugar, are in almost the same concentrations in the two fluids. Chloride is unequally distributed in the aqueous and the serum, the former having a considerably higher concentration; this point will be discussed in the next section.

THE FORMATION OF THE INTRA-OCULAR FLUIDS.

There have been three theories proposed in respect to the formation of intra-ocular fluid, namely, that the process is one of (a) *dialysis*, (b) *filtration* or (c) *secretion*. The results of the experiments of Duke-Elder and his associates upon the concentrations of electrolytes in the aqueous humor and in the blood serum leave little doubt that the proc-

ess is one of dialysis. They found that the distribution of the ions Na, K and Cl between the two fluids is in accordance, approximately, with that demanded by Donnan's equilibrium theory (p. 103) and with the laws of simple dialysis. In experiments upon the surviving heads of cats perfused with cat's blood containing an excess or a deficiency of one or other of these ions the permeability of the membrane separating aqueous humor and blood was approximately the same before as after poisoning with cyanide, and the same as in the normal animal. Such results seem definitely to exclude a secretory process.

The surface of the ciliary body and the posterior aspect of the iris are believed to constitute the membrane interposed between the aqueous humor and the blood. That diffusion occurs across *both* these surfaces is indicated by the following observations. When the pupillary aperture is occluded either experimentally or as a result of disease, aqueous fluid accumulates behind the iris. On the other hand, fluid is formed after excision of the iris or when it is congenitally absent. In certain fish not possessing a ciliary body and in the congenital absence of the latter in man, normal aqueous humor is present; it has also been found in a cyst of the iris itself.

THE CIRCULATION OF THE INTRA-OCULAR FLUIDS. THE DRAINAGE SYSTEM OF THE EYE. Intra-ocular fluid is probably reabsorbed to some extent from all parts of the interior of the globe. A small proportion of the secreted fluid passes from the posterior chamber through the zonule and down the hyaloid canal to the lymphatics of the optic nerve. However, less than 1 per cent is reabsorbed in this way, or indeed from any region of the eye lying posterior to the iris. The chief exits for the fluid are at the angle of the anterior chamber (*angle of the iris* or *filtration angle*) and from the anterior surface of the iris. It will perhaps be of advantage to the reader if the main structural features of this region are recalled.

On the deep aspect of the sclera at its junction with the cornea and in front of the angle of the anterior chamber lies an annular venous sinus—the *canal of Schlemm* (*sinus venosus sclerae*) (fig. 448). The sinus completely surrounds the corneal margin and in meridional sections of the eye appears as a small oval gap or cleft lined by endothelium. The inner or posterior wall of the canal is separated from the anterior chamber by a zone¹ of trabecular tissue formed by the breaking up of the posterior elastic lamina of the cornea and termed the *pectinate ligament*; the intervals between the trabeculae are termed the *spaces of Fontana*. The tra-

becular tissue of the pectinate ligament is continued around the irideal angle, its fibers terminating in the tissue of the iris. Schlemm's canal is fed by an *afferent arteriole* derived from the ciliary arteries and drained by an *efferent venule* which empties into the episcleral venous plexus (Friedenwald). The spaces of Fontana communicate with the anterior chamber, but there is no *direct* communication between the former and the lumen of Schlemm's canal; the canal cannot be injected, for example, with a colloidal solution introduced into the anterior chamber.

The *scleral spur* is the term applied to a small triangular projection of the sclera on the posterior aspect of the sclerocorneal junction; it lies immediately behind the outer part of the posterior wall of Schlemm's canal and gives attachment to the meridional fibers of the ciliary muscle. Contraction of the muscle, by pulling upon the spur, is said to dilate the canal and thus favor the drainage of fluid from the anterior chamber.

Movement of the intra-ocular fluid from the posterior to the anterior chamber and from the latter to the filtration angle is brought about largely through intermittent variations in intra-ocular pressure occasioned by the several factors already discussed (e.g., pulsatile and respiratory variations in blood pressure and actions of the eyelids, etc.). Temperature differences between the superficial and deeper parts of the anterior chamber (*thermal factor*) cause convection currents to be set up which also play an important part in the movement of fluid. At the angle of the iris the fluid percolates into the spaces of Fontana whence it is absorbed across the posterior wall of the canal of Schlemm.

Friedenwald and Pierce have demonstrated a differential absorption between the water, crystalloids and protein constituents of the aqueous. From their experiments which involved the introduction of substances into the anterior chamber, these observers conclude that crystalloids and a small quantity of water are reabsorbed from the anterior surface of the iris, passing by diffusion through the walls of the capillaries. Colloids are removed by the phagocytic action of the surface layer of epithelial cells. A part of the protein is hydrolyzed by the action of enzymes present in the fluid and reabsorbed as amino-acids. Water is absorbed chiefly through the spaces of Fontana and the canal of Schlemm. The rate of passage of fluid through the wall of the canal is governed apparently by hydrostatic and osmotic forces. The pressure of blood in Schlemm's canal (or rather in the small veins leading from it) is stated to be equal to or about 1 mm. higher than that of the fluid in the anterior chamber, but after the absorp-

tion of crystalloids one would expect the osmotic pressure of the aqueous to be considerably lower than that of the serum; under such circumstances an uptake of fluid would occur, provided the blood flow through the canal did not fall below a certain level. Slowing of the circulation would tend (as a result of the dilution of serum colloid dilution by the reabsorbed fluid and consequent reduction in osmotic pressure) to reduce the rate of reabsorption, an increase in blood velocity to increase it. Such a relationship was actually observed by Friedenwald and Pierce. Increase in intra-ocular pressure would quite evidently increase reabsorption, the pressure would thus tend automatically to be restored to its original level.⁸

GLAUCOMA OR OCULAR HYPERTENSION. Persistent elevation of the intra-ocular pressure occurs as an accompaniment of several diseased states of the eye and may then be due to blockage of the drainage channels at the iridial angle or to the excessive production of fluid. The latter effect may result from mechanical irritation of the ciliary processes (e.g., by displacement of the lens) or obstruction of the venous channels with consequent rise in capillary pressure. Ocular hypertension associated with some such obvious disease of the eye is referred to as *secondary glaucoma*. When the intra-ocular pressure is persistently elevated above 35 mm. or so and no abnormality of the eye exists to account for the hypertension, it is termed *primary glaucoma*. At the outset it may be said that, though primary glaucoma has been the subject of much speculation, its cause remains obscure.

The excessively high intra-ocular tension causes compression of the vessels and in time serious disturbances in the nutrition of the eye result, namely, optic atrophy, excavation ("cupping") of the disc, blindness and ultimately disintegration of the optical mechanism. Owing to the readjustments which take place in the ocular circulation the hypertension may exist for some time before any of these effects make their appearance. The pressure as it gradually rises first compresses the venous channels but, as a result of the opening up of the arterioles and capillaries, a larger proportion of the arterial pressure is transmitted to the venous side; the compressing force is thus overcome and the circulation

⁸ According to some authorities (Maggiore, Duke-Elder) the canal of Schlemm contains blood only when the ocular venous pressure is inordinately high, being filled under usual circumstances with an aqueous fluid (with an osmotic pressure around that of the fluid in the anterior chamber). Since, as mentioned above, the pressure of blood in the small veins leading from it is higher than the normal intra-ocular pressure the canal could not serve as a pathway for the continued reabsorption of fluid; it is claimed that reabsorption can occur only if the intra-ocular pressure rises above the normal level. This conception attributes a safety-valve function to the canal, i.e., it is called into play presumably only in an emergency.

maintained. This stage in the progress of the condition is referred to as *compensated glaucoma*. A point will be reached, however, at which the pressure of the intra-ocular fluids approaches equality with that in the ophthalmic artery; then further compensation becomes impossible and the structural changes just mentioned supervene. The condition is then termed *inflammatory* or *decompensated glaucoma*.

The possible factors which have been suggested in explanation of the elevated pressure will be briefly considered. Mechanical obstruction at the filtration angle, due to reduction in the depth of the anterior chamber and the consequent adhesion of the periphery of the iris to the cornea, is frequently present in decompensated cases, but this is secondary and not primarily related to the hypertension. It is not improbable that some abnormality in the nervous control of the vascular bed of the globe is fundamentally responsible. Friedenwald suggests that the reabsorption of water through the mechanism of Schlemm's canal as a result of sclerosis and narrowing of the afferent vessels (p. 1004) may be the essential factor concerned. Reduction in the caliber of these vessels would tend, by slowing the blood flow through the canal, to reduce the reabsorption rate. Spasm of the vessels feeding the sinus would have a similar effect. On the other hand, the reduced depth of the anterior chamber in decompensated glaucoma suggests that the increased pressure originates in the

posterior chamber of the eye and the theory has been advanced that swelling of the vitreous is responsible. From the gel-like nature of the vitreous body one might expect its water content to vary with changes in its inorganic constituents or in pH. It has been found, however, that the chemical changes necessary to cause any significant increase in volume of the vitreous are far greater than any that could occur in the body. Finally, a vasodilator toxin of the histamine type has been suggested which supposedly, by causing dilatation of the intra-ocular capillaries and an increase in the permeability of their walls, would lead to overproduction of intra-ocular fluid. The aqueous in decompensated glaucoma has a higher protein, and lower chloride content and osmotic pressure than normal; this fact lends some force to the theory of increased capillary permeability. The abnormal permeability would also, by reducing the effective osmotic difference between the contents of the anterior chamber and the blood, tend to diminish reabsorption. Nevertheless, analysis of the aqueous humor in *compensated* cases shows no significant departure from the normal and therefore lends no support to the idea that a change in capillary permeability is the fundamental factor in the development of glaucoma.

There is no causative relationship between arterial and ocular hypertension (see p. 1002).

CHAPTER LXXVII

THE VISUAL FIELDS AND PATHWAY. MOVEMENTS OF THE OCULAR MUSCLES. STEREOSCOPIC VISION

THE VISUAL FIELDS. The visual field of one eye is the part of the external world which is seen by that eye at any given moment, i.e., when its

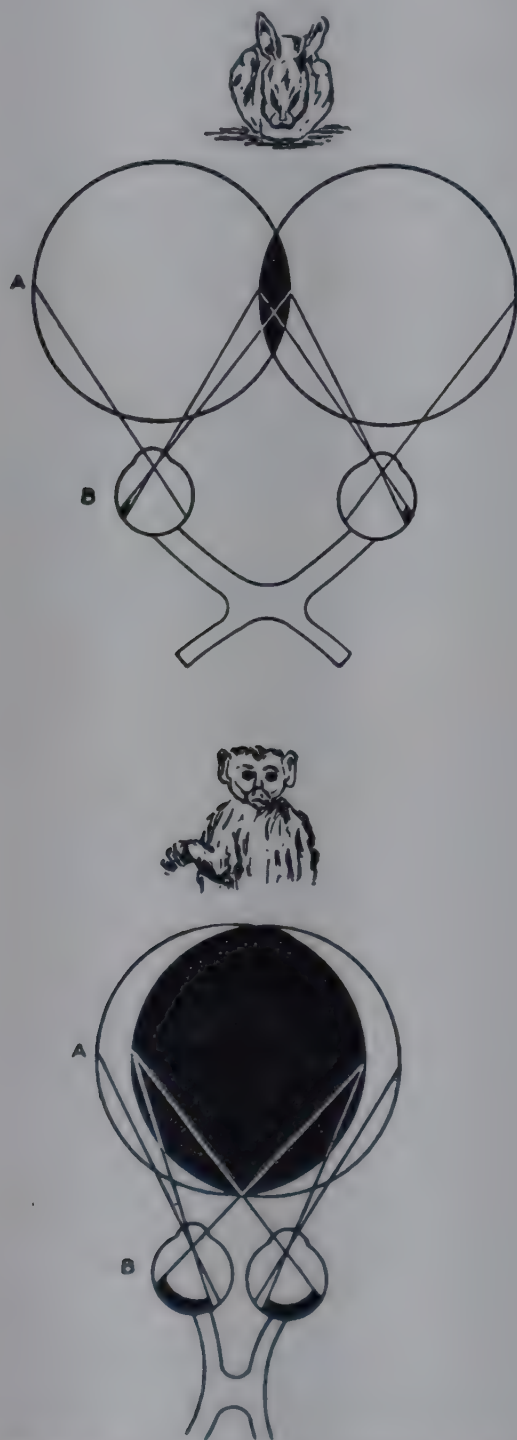


FIG. 462. Showing monocular (white) and binocular (black) fields of vision. Upper rabbit; lower monkey (or man) (from Parsons, after Brouwer and Zeeman).

gaze is fixed in one direction. It may be likened to a portion of a great hollow sphere—a bowl—upon the interior surface of which the images of the external world are projected. Traquair pictures

the visual field as “an island of vision surrounded by a sea of blindness”; carrying the simile further, the surface contour of this imaginary island is described in terms of visual acuity, the highest point corresponding to the fovea, a deep (bottomless) point to the blind spot and a gradual slope to the coastline, to the peripheral retina. The visual field of each eye subtends an angle of about 160° in the horizontal and 145° in the vertical meridian. The visual field of each eye is divided by a line passing vertically through the fixation point (p. 1017) into two unequal parts, an outer or *temporal* and an inner or *nasal*. The latter is smaller owing to the shadow of the nose, its diameter being about 60° whereas the diameter of the temporal part



FIG. 463. The blind spot. Close the left eye, hold the figure about six inches in front of the right eye and look steadily at the cross. Move the book slowly toward the eye until the circle disappears. When this occurs the image of the circle has fallen upon the entrance of the optic nerve from which rods and cones are absent; it is therefore insensitive to light. Figure on the right shows the blind spot projected 6" in front of the right eye as mapped out by means of perimetry (After Helmholtz.)

around 100° . Similarly a line passing horizontally through the point of fixation divides the field into an upper and a lower part, the former being restricted by from 5° to 10° by the upper lid and orbital margin. Rays of light from the outer or temporal half of the visual field fall upon the nasal (inner) half of the retina, those from the inner or nasal half of the visual field fall upon the temporal half of the retina (fig. 467, p. 1011). Although an image is formed upon each retina the two are fused in consciousness into a single impression (See p. 1014). In most animals the visual fields of the two eyes overlap, that is, certain parts of the outside world are seen by both eyes at the same instant—*binocular vision*. In animals with eyes placed laterally in the head overlap of the visual fields must obviously be very small in extent, the

visual fields being almost completely separate—*monocular vision*. The extent of overlap of the visual fields of the monkey and of man, whose eyes are placed in the front of the head, is large (120° horizontal diameter) and the monocular field of vision, that is, the field which can be seen by one eye but not by the other, is relatively small (35°) (figs. 462 and 465). Rays of light entering the eyes from an object in the binocular field of vision fall upon the nasal half of one retina and upon the temporal half of the other. If, however, the object is well to the right or to the left of the line

two fields plus the monocular fields on each side is about 200° .

We shall see when the arrangement of the fibers conveying visual impulses is considered that fibers arising from the nasal halves of the peripheral retinas and of the maculae cross in the chiasma, whereas the temporal fibers remain uncrossed. Thus it is that the occipital cortex of one side receives impulses from the nasal half of the opposite retina and from the temporal half of the retina of the same side (fig. 467, p. 1011). Loss of vision in one half of each eye is called *hemianopia*¹ (half-blindness). When the blindness affects the right

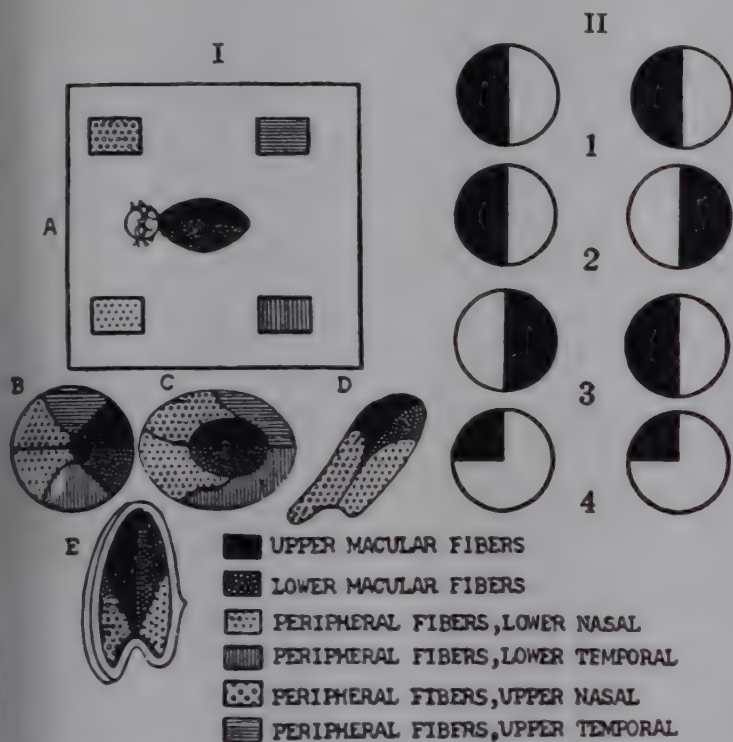


FIG. 464. I, showing the distribution of the visual fibers in the retina (A), optic nerve (B), chiasma (C), optic tract (D) and in the lateral geniculate body (E). In D the area marked with small circles represents the fibers of upper half of peripheral retina, the crosses the lower half (redrawn from Duke-Elder, after Henschen and Brouwer and Zeeman). II, Diagram of types of hemianopia, 1, homonymous; 2, bitemporal; 3, binasal; 4, homonymous superior quadrantic.

of vision, i.e., in the outer part of either temporal field, the rays then fall upon the nasal half of the peripheral retina of the nearer eye (right or left) but not upon the other retina which is shaded by the nose. So the monocular field of vision consists in man of a crescentic area (35°) at the outer limit of the temporal field of each eye. When one looks directly at an object the eyes are turned so as to bring an image of the object upon the most sensitive area of each retina, i.e., upon the nasal and temporal halves, respectively, of the maculae luteae. The horizontal diameter of the entire visual field, that is, of the area of overlap of the

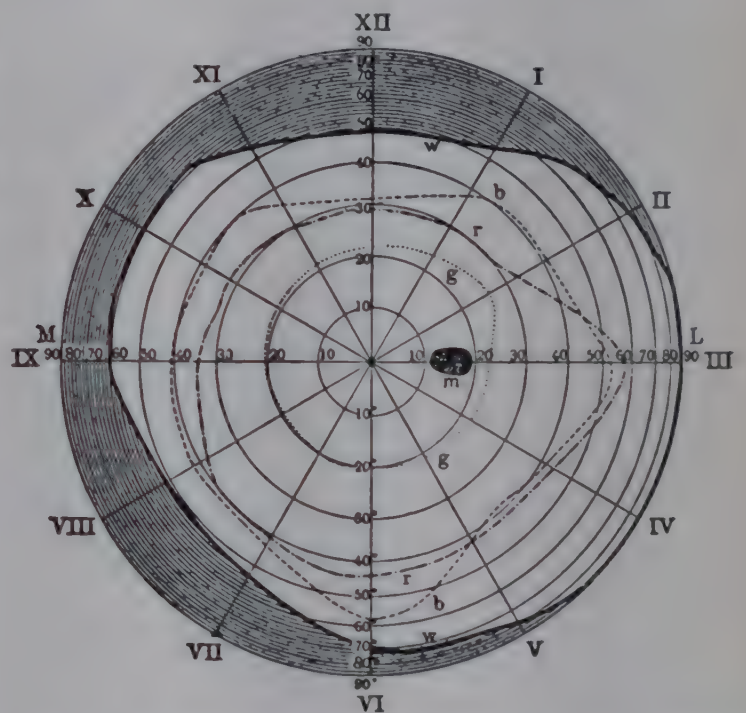


FIG. 465. Perimeter chart showing normal visual field of left eye. M, blind spot; g, r, b and w indicate boundaries of fields for green, red, blue and white, respectively. Meridians indicated by Roman numerals. (After Starling.)

or the left halves of both retinas, i.e., the nasal half of the left retina (temporal half of visual field) and the temporal half of the right (nasal half of the visual field) or vice versa, the hemianopia is said to be *homonymous*—left or right respectively. If the blindness is in the *left* half of one retina and in the *right* half of the other, i.e., in either both temporal retinal halves (nasal halves of visual fields) or in both nasal retinal halves (temporal halves of visual fields) the hemianopia is referred to as *binasal* or *bi-temporal*, respectively. It will be noted that the qualifying terms refer to the affected

¹ Hemiopia (half sight) and hemiopia are alternative terms which are sometimes used; they have practically identical meanings.

halves of the *visual fields* and not to the retinal halves. In other instances a quarter only of each visual field is affected, when the term *quadrantic hemianopia* is employed. It may be the upper or the lower quadrants of the nasal or of the temporal fields which are involved, or homonymous quadrants may be affected, i.e., a quadrant in the nasal field of one eye and in the temporal field of the other. The type of hemianopia is further specified by the use of the word "superior" or "inferior" (fig. 464). Thus, a superior nasal quadrantic hemianopia is one in which the eyes do not see objects in the upper nasal quadrants of the visual fields, (blindness of lower temporal retinal quadrants).

Isopters. The sensitivity of the retina from the periphery to the fovea can be explored by using a series of test objects of graduated sizes with the perimeter, and determining in different meridians the distance from the fixation point (p. 1017) at which each object is just perceptible. The points so determined are marked upon the perimeter chart and lines drawn through each set. Thus a series of boundary lines roughly concentric with the fovea are constructed which indicate the thresholds for the perception (minimum visible, p. 961) of the different test objects, and therefore demarcate levels of retinal sensitivity. Each is called an *isopter of sensitivity*; they might be compared to the contour lines indicating elevations on a detailed geographical map.

THE BLIND SPOT. The entrance of the optic nerve (p. 956) since it is devoid of rods and cones is completely blind. An object whose image falls upon it is therefore invisible (see fig. 463). Not even a sensation of blackness results, for when the eye is fixated upon the cross, as described in the legend of the figure, and the book moved until the optic disc is occupied by the circle the latter simply disappears, no sensation whatever being experienced to indicate its existence. Ordinarily this "hole" in the visual field causes no inconvenience because, in any position of the eyes, should one image of an object fall upon the blind spot a sensitive part of the opposite retina receives the other image. But even when one eye is closed the fine involuntary ocular movements, by constantly shifting the fixation point, though ever so slightly, keeps us completely unaware of the existence of the insensitive area. When mapped out accurately by perimetry the blind spot has the shape shown in figure 463.

THE OPTIC NERVE. The ganglion cells of the retina (ganglion cell layer) whose central processes constitute the optic nerve, are the secondary neurons of the visual pathway (p. 955). The primary neurons are the bipolar cells of the inner nuclear layer, the peripheral processes of the

latter connecting with the visual receptors—the rods and cones. Tertiary neurons complete the pathway from the lateral geniculate body to the visual cortex. The fibers of the ganglion cells as they enter into the formation of the optic nerve are arranged in groups corresponding, in their relative positions, to the quadrants of the peripheral retina from which they arise. That is, fibers from the upper and lower temporal quadrants of the retina are found in the upper and lower parts of the nerve, respectively (fig. 464). Those from the nasal quadrants are situated in the inner sections of the nerve, the fibers from the upper quadrant lying above those from the lower. The macular fibers occupy a lateral position, being wedged between the upper and lower temporal bundles, but again, fibers from the upper half of the macula lie above those from the lower half.

THE OPTIC CHIASMA. The fibers from the temporal halves of the peripheral retina continue uncrossed into the corresponding optic tracts, while the fibers from the nasal halves cross in the chiasma to the optic tract of the opposite side.² As the fibers of the optic nerve approach the chiasma the macular fibers move toward the center or "core" of the nerve. In the chiasma itself the temporal fibers lie in its lateral angle. Those of upper retinal origin lie above those arising from the lower retinal quadrant. In the crossing of the nasal fibers, those from the upper quadrants lie upon the upper aspect, those from the inferior quadrants upon the under aspect of the chiasma; the macular fibers lie in between.

Perimetry is the term applied to the procedure of mapping out the visual fields. The instrument employed is called a *perimeter*. It comprises a metal band or arm, shaped in a large arc of a circle with its concavity directed towards the subject. A holder sliding in the arc carries the test object which can be moved centrally or peripherally as required. The arm itself is pivoted at the center enabling it to be rotated to any angle. The subject's head is supported on a chin-rest. One eye is covered; the eye under examination is placed at the center of the sphere of which the perimeter arm forms the arc, and made to fix a point straight ahead in the center of the arm. The latter is rotated by degrees through a full circle and at each new position the test object is moved centrally until it is just perceived by the subject. This point and corresponding points at the various positions of the arm are marked upon a perimeter chart and the contour of the visual field outlined through them. The chart

² In animals such as the rabbit in which vision is largely monocular, the uncrossed fibers are very few in number.

(fig. 465) is ruled in circles (comparable to latitudes on a geographical map) to indicate degrees from the point of fixation, and in radiating lines ("longitudes" or meridians). The mapping of the blind spot and of the sensitivity of the retina in isopters has been referred to. The reader should consult texts on ophthalmology for a more detailed description of perimetry. A simple but rough method of perimetry (*confrontation method*) which will reveal a major limitation of the visual fields is the following. The observer stands facing the subject and about two feet in front of him. The patient covers one eye while the other, which he fixes upon the opposite eye of the examiner, is being tested. The examiner holds his finger midway between himself and the patient but outside the limit of his own visual field and then brings it slowly toward the mid-line. The observer compares the position at which he first sights his finger with that at which it is first seen by the patient. The procedure is repeated from various directions, above, below and from either side.

The optic tract and primary optic centers

The visual pathway from the chiasma to the primary optic center consists of compact bundles of fibers—the *optic tract*. In the optic tract bundles of nasal and temporal fibers intermingle, but those from the upper quadrants of the peripheral retina tend to lie ventro-laterally, those from the lower quadrants ventro-medially. The macular fibers lie dorso-laterally. The optic tract passes backwards and outwards between the tuber cinereum and the anterior perforated substance to the cerebral peduncle around which it turns as a flattened band to reach the *external (lateral) geniculate body*.³ In this, the *primary visual center*, the great majority of the optic fibers end. A smaller number are continued to the *superior colliculus* (superior corpus quadrigeminum) but

none of these are of macular origin. The superior colliculus serves as a center for light reflexes and for the correlation of impulses from the retina with movements of the skeletal muscles, but apparently not for sight. The pulvinar of the optic thalamus has been generally looked upon as a relay station for visual impulses, but the researches of Brouwer and Zeeman lend no support to this belief; in monkeys, no degenerated fibers were observed to end in the pulvinar after excision of the eyeball. It has also been stated by Henschen that a lesion of the pulvinar in man does not cause hemianopia, whereas disease involving the external geniculate body but which spares the pulvinar produces complete hemianopia. The pulvinar may, however, be concerned with eye movements and visual judgments, e.g., the recognition of depth (stereoscopic function) and distance. Its connection with the angular gyrus which is a center for eye movements suggests that it serves these functions, but in order to do so it would require to be in communication also with the visual area of the cortex or with the external geniculate body. Such connections have not been demonstrated.

The *optic radiation (geniculocalcarine pathway)*. The visual fibers after leaving the external geniculate body pass through the posterior extremity of the internal capsule, and curving forward and outward into the temporal lobe sweep backward in relation to the outer aspect of the posterior horn of the lateral ventricle to reach the *area striata* (area 17) of the occipital cortex (pp. 886 and 896). The optic radiation also contains descending fibers which end in the superior colliculus and the external geniculate body.

The *visual cortex*. This comprises that part of the cortex referred to above as the area striata, which forms the walls and lips of the calcarine fissure on the mesial aspect of the occipital lobe. The different retinal areas in their projections upon the cortex show definite localization. The homonymous halves of the peripheral retinas are represented in the anterior three-fourths of the visual area, the upper quadrants in the upper wall and lip, the lower quadrants in the lower wall and lip. In other words, the nasal half of the right retina and the temporal half of the left are projected on to the left occipital cortex—the projection of the upper quadrant in each case lying above that of the lower quadrant. Similarly, the nasal half of the left retina and the temporal half of the right are projected on to the right striate area. The macular representation is less extensive. It occupies the posterior part of the striate area

³ The projection of the retina upon the external geniculate body has been studied by Brouwer and Zeeman in monkeys. These observers produced localized lesions in the retina and examined the geniculate body histologically after time had been allowed for degeneration of the optic fibers. It was found that the retinas were not projected diffusely throughout the primary optic center, but showed localization of their different regions to definite sections. Thus the upper parts of the peripheral retinas, both nasal and temporal, of the two eyes were projected to the medial parts of the geniculate body. The lower parts of the retinas were represented in the lateral part (fig. 464, E). Dorsal to these regions and wedged between them was an extensive area wherein the macular fibers terminated. Binocular and monocular types of vision have separate representations. In the monkey the area which receives fibers from only one eye is very small, occupying a small rim on the ventral aspect of the primary center. In the rabbit, on the other hand, the monocular projection occupies almost the entire geniculate body, binocular vision being represented by a narrow area on the medial aspect of the geniculate body.

reaching backwards to the occipital pole, but it also spreads forwards to overlap the projection area of the peripheral retina (fig. 466). As in the case of the peripheral retina, the upper and lower parts of the macula are projected to the upper and lower halves, respectively, of the striate area. The cortical projection of the macula is possibly bilateral,⁴ i.e., represented in its entirety in both hemispheres, since the retention of macular vision in both eyes after destruction of the pole of one occipital lobe has been reported (Brouwer).

fibers in the outer angle of the chiasma, as by an aneurysmal dilatation of the internal carotid artery, may produce blindness in the temporal part of the retina of the same side. If these fibers on both sides are affected, the sight in the temporal half of each retina may be lost (*bi-nasal hemianopia*). According to Cushing a dilated third ventricle may, by pressing from above, force the angles of the chiasma against sclerosed internal carotid arteries and so produce a bi-nasal hemianopia. (b) Pituitary tumors, owing to the

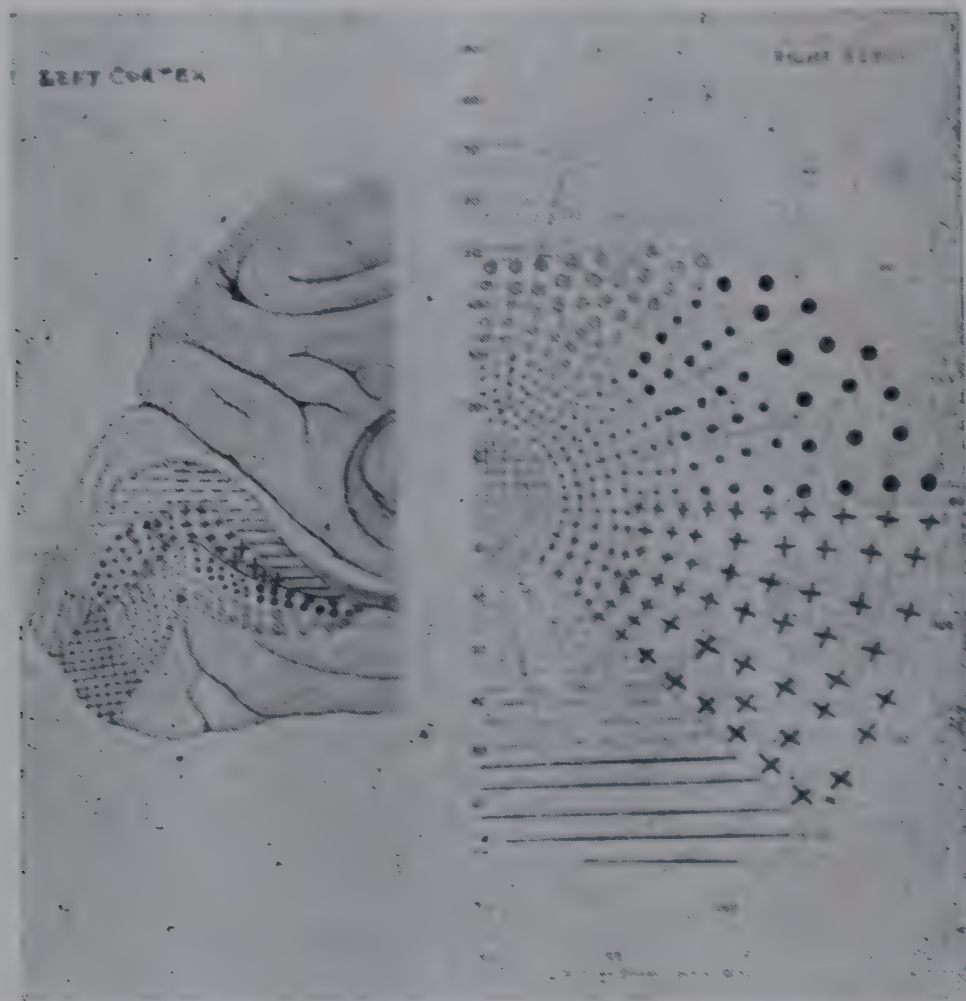


FIG. 466. Diagram showing the projection of the retina on the calcarine cortex (from Holmes). Right half figure is temporal half of right visual field (p. 1637).

The effects of lesions at different levels of the visual pathway (see also p. 1013)

(1) A destructive lesion of one optic nerve will result in total blindness of the corresponding eye (fig. 467). Increased intracranial pressure may cause atrophy of the optic nerves and a gradual concentric reduction of the visual fields of both eyes.

(2) A lesion involving the chiasma will result in visual defects whose nature will depend upon the fibers destroyed. (a) Pressure upon the uncrossed

position, are likely to involve the nasal fibers at the point of their crossing and thus cause *bi-temporal hemianopia*. Since the nasal fibers from the lower retinal quadrants lie ventral to those from the upper, the lower are likely to be involved first in pituitary tumors; *superior temporal quadrant hemianopia* will result. Lesions (e.g., tumor pressing from above tend first to cause defects in the lower temporal quadrants of the visual field. Dilatation of the third ventricle or a tumor of the pituitary stalk may produce such an effect.

(3) Lesions of the optic tract, of the primary visual center or of the optic radiation will result in *homonymous hemianopia*. The right halves

⁴ For views on this question see Penfield and associates, *Arch. Neur. Psych.*, 1935, 33, 816, and Maison and associates, *ibid.*, 1938, 40, 981.

the two eyes (left halves of the visual fields) being effected in right-sided lesions and the left halves in left-sided lesions. An abscess or tumor of the temporal lobe may, by involving the optic tract or optic radiation, cause a homonymous hemianopia. When the optic radiation is pressed upon by a

(4) *Lesions of the occipital cortex.* A lesion involving the area striata of one hemisphere or the optic radiation before their termination therein results in an homonymous hemianopia, right or left, depending upon the side of the brain affected. Quadrantic homonymous hemianopia will result when the lesion is restricted to the upper or lower part of the striate area. Owing to the large cortical area representing the macular region, or perhaps to the fact that the macula is bilaterally represented, extensive occipital lesions or excision of a large part of this area often leave acute (central) vision intact, the blindness then involving only the peripheral half of each retina.

PUPILLARY REFLEXES

Reflex changes in the size of the pupil occur under the following conditions: (a) Constriction or dilatation occurs in response to changes in light intensity (light reflex). When light is thrown into the normal eye the pupil of that eye constricts promptly; this is the *direct pupillary reaction*. The pupil of the opposite eye, though shaded, also narrows; this, the *indirect or consensual pupillary reaction*, is dependent upon fibers which cross to the pupillary-constrictor center of the opposite side. (b) Constriction occurs as a part of the mechanism of accommodation to near vision (pupillary reaction of accommodation). With it are associated convergence of the eyes and accommodation of the lens. These three associated reactions are appropriately grouped under the term *near reflex* or *accommodation reflex*. (c) Dilatation follows stimulation of the skin of the neck (ciliospinal reflex). (d) Dilatation may occur during certain emotional states (e.g., fear), as a result of acute pain or a sudden sound. The pupil is extremely sensitive to the latter type of stimulus, responding by dilatation to sounds of different pitches at the lowest intensities which can be heard. (e) Finally, stimulation of labyrinthine receptors causes changes in the diameter of the pupil (p. 844). For example, rapid rotation of the body around its long axis causes dilatation of the pupil and rhythmical changes in its diameter (*hippus*).

THE PUPILLARY MECHANISM

The iris is the most anterior part of the vascular tunic of the eye. It is a thin contractile disc perforated a little to the nasal side of its center by the pupil. The pupillary margin rests upon the anterior surface of the lens. The space between the lens and the cornea is divided by the iris into a larger *anterior* and smaller

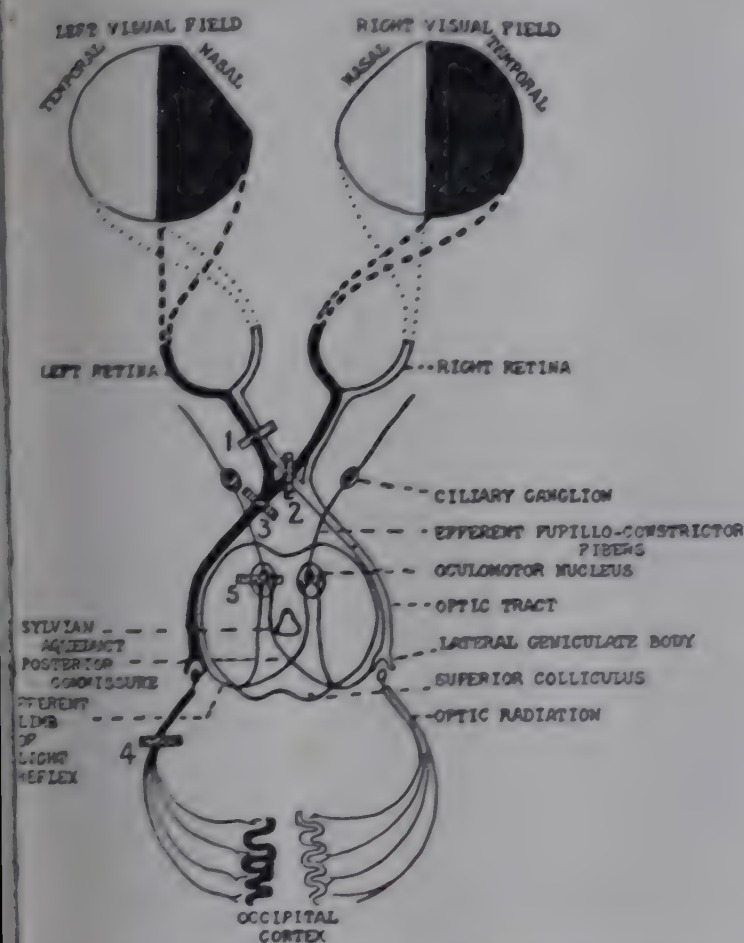


FIG. 467. Diagram to show the effects upon vision and pupillary reactions resulting from interruption of retinal impulses at various levels. 1, Optic nerve; blindness of corresponding eye, direct reaction of this eye and consensual reaction of sound eye lost. Consensual reaction of blind eye and direct reaction of sound eye retained. Near reflex unaffected. 2, Chiasma; bitemporal hemianopia. Wernicke's pupillary reaction. 3, Optic tract; homonymous hemianopia (blindness in nasal half of right retina and temporal half of left). Wernicke's pupillary reaction. 4, Optic radiation; homonymous hemianopia, light and near reflexes retained. 5, At synapses in the oculomotor nucleus. Light reflex lost, near reflex retained (Argyll-Robertson pupil, see also p. 1014). The lesion is usually bilateral (as in tabes, disseminated sclerosis, etc.); the afferent pupillary pathways are probably involved at their decussation in the midbrain.

temporal lobe lesion the hemianopia is very often complete, i.e., quadrantic. The ventral fibers of the radiation are likely to be implicated by a tumor in the lower part of the lobe, and a superior quadrantic hemianopia result. Injury to the nasal fibers tends to cause a defect confined at first to the lower homonymous quarters of the visual fields.

posterior chamber, the two chambers communicating through the pupil. The periphery (root) of the iris is attached to the anterior surface of the ciliary body and is continuous through the pectinate ligament (p. 1003). with the posterior elastic lamina of the cornea. The following five layers from before backwards compose the structure of the iris, (a) the anterior epithelium, (b) the anterior limiting membrane, (c) the stroma, (d) the posterior membrane and (e) the posterior epithelium. The *anterior epithelium* consists of a single layer of flat endothelial-like cells. Near the pupillary margin of the iris there are many small pits—the *crypts of Fuchs*—over which the epithelium is absent. The stroma is composed of loose connective tissue. It transmits the vessels and nerves and holds numerous branched cells which in dark eyes contain pigment granules. The iris contains two involuntary muscles—the sphincter pupillae and the dilator pupillae. The *sphincter pupillae* is embedded in the stroma and comprises a band of circular fibers about 1 mm. broad surrounding the pupil. When these fibers contract the pupil is constricted. The *dilator pupillae* constitutes the fourth layer of the iris, i.e., the posterior membrane, mentioned above. It consists of a thin layer of smooth muscle fibers which converge towards the pupillary margin where they blend with the fibers of the sphincter. At the root of the iris the dilator fibers pass into the ciliary body from which they take origin; when they contract they draw upon the pupillary margin and thus dilate the pupil. The *posterior epithelium* comprises two layers of deeply pigmented cubical cells; it is the continuation anteriorly of the pars ciliaris retinae (p. 993). The arteries of the iris form two vascular circles, one near the pupillary margin—the *circulus arteriosus minor*, the other near the root of the iris—the *circulus arteriosus major*. The two circles are connected by vessels which, arising from the larger circle, converge towards the pupillary margin where they form the smaller circle.

Blue or gray eyes owe their appearance to the pigment in the posterior epithelial layer as seen through the unpigmented stroma and other layers of the iris. The pigment cells of the stroma are responsible for the color of dark eyes, the shade varying with the quantity of pigment present. In the white races nearly all new-born babies have blue eyes because pigment does not develop in the stroma until some weeks after birth. But negro babies and others belonging to the dark races have brown eyes, the stroma pigment being well developed at birth.

Pupillo-constrictor pathways

It is generally believed that the receptors (cones but not the rods) of the light reflex are the same as those mediating visual sensations. It is likely that the pupil is under the control of nerve fibers activated by both rods and cones. Wagman and his associates have made the interesting observa-

tion that in dim light the curve of pupillary size at different intensities of a monochromatic light agrees closely with the visibility curve of the dark adapted human eye. The central connections of the afferent fibers of the pupillary mechanism are different from those of the visual fibers. They part company from the latter at the level of the primary visual center (lateral geniculate body). They do not traverse the latter but are continued through the brachium of the superior colliculus to the oculomotor nucleus on both sides of the brain. The superior colliculus itself is not interposed in their path, for Ranson and Magoun did not observe pupillary constriction when this part was stimulated. The partial decussation of the afferent fibers, occurs, Ranson and Magoun believe, in the posterior commissure. An earlier crossing of some fibers occurs also in the optic chiasma. Though under ordinary circumstances reduction in the tone of the pupillo-dilator center occurs reciprocally with activation of the pupillo-constrictor center, the light reflex can be carried out through the latter alone. The reflex is therefore retained after section of the cervical sympathetic (which conveys the dilator fibers). Since the afferent fibers mediating the light reflex separate from the visual pathway at the level of the lateral geniculate body, lesions of the optic pathway beyond this point do not interfere with the light reflex.

The *efferent* pupillo-constrictor pathway is constituted of parasympathetic fibers which arise in the oculomotor nucleus (probably the Edinger-Westphal nucleus) and are conveyed to the iris (sphincter pupillae) via the third nerve, ciliary ganglion and short ciliary nerves (fig. 468). The *near reflex* is dependent upon cortical centers. Impulses pass by association fibers from the occipital to the frontal cortex and thence via the internal capsule to the nucleus of the 3rd nerve. Peripheral to this the efferent pathway is the same as that for the light reflex. The afferent pathway is via the visual fibers i.e., external geniculate body and optic radiation, not through the superior colliculus. The reflex is bilateral, i.e., it occurs in both eyes when one is covered and the other directed to a near object.

DILATOR PATHWAYS. The dilator muscle receives sympathetic fibers which arise from the 8th cervical and the 1st and 2nd thoracic segments of the spinal cord and pass via the cervical sympathetic to the superior cervical ganglion. From here postganglionic fibers are conveyed along the

internal carotid artery into the cranial cavity. Entering the trunk of the nasociliary branch of the first division of the fifth nerve, they are transmitted to the iris in the long ciliary nerves. Some fibers also pass without interruption through the ciliary ganglion into the short ciliary nerves. These fibers supply in addition the smooth muscle of the orbit which lies in relation to the capsule of Tenon (fascia bulbi) and in the "check ligaments" of the ocular muscles. The smooth muscle forming the deep layer of the levator palpebrae superioris also receives innervation from the sympathetic. A higher pupillo-dilator center is situated in the hypothalamus (p. 883). This

When the sympathetic fibers are paralyzed the pupil is narrowed as a result of the unbalanced action of the constrictor fibers, and the dilatation of the pupil which normally follows the application of a stimulus, such as a scratch or pinch, to the skin of the neck (ciliospinal reflex) fails to occur. The pupil, however, still reacts to light. Drooping of the upper lid (ptosis) will result from paralysis of the smooth muscle of the levator palpebrae superioris and there may be recession of the eyeball (enophthalmos) from paralysis of the unstriated muscle of the orbit (see p. 951).

An investigation of the pupillary reactions may give valuable information concerning the site of a

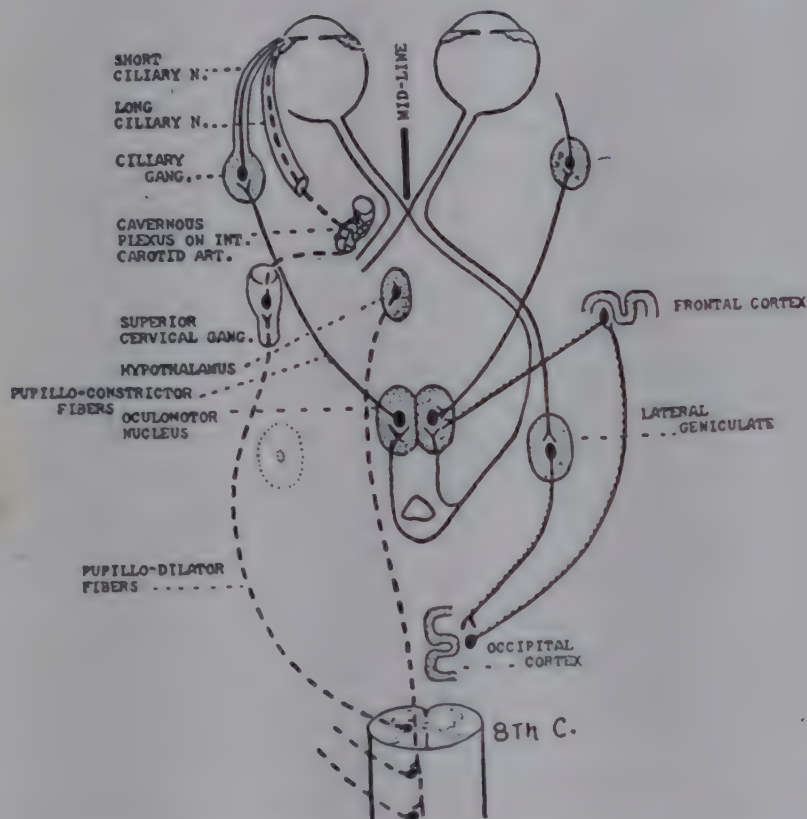


FIG. 468. Diagram to illustrate pupillary reflexes. Interrupted lines indicate the dilator reflex, plain lines the constrictor reflex and visual pathway to the level of the lateral geniculate body; hatched lines show path of near reflex from lateral geniculate body to the cortex and nucleus of the 3rd nerve.

center in turn is probably connected with the cortex of the frontal lobe. It sends fibers through the midbrain which, according to the researches of Beattie, pass ventrally to the posterior commissure to enter the superior colliculus, thus coming into close relationship with the afferent pupillo-constrictor fibers. The pathway is continued downwards through the reticular formation of the pons and medulla to the spinal center. The pupillo-dilator reflex involves reciprocal inhibition of pupillo-constrictor tone. This is the paramount factor in the dilator reflex, for after section of the sympathetic pupillary fibers, the pupil dilates in the dark, or in response to a painful stimulus or emotional excitement, in an almost normal fashion.

lesion in the brain (see fig. 467, p. 1011). (a) A lesion destroying one optic nerve, since it interrupts the afferent pathway but leaves the efferent intact, abolishes the direct but not the indirect (consensual) reaction on the blind side. The direct reaction on the sound side is, of course, retained but the indirect is lost. That is to say, a light thrown into the sound eye causes a response in this eye as well as in the blind eye, but a light thrown into the blind eye is without effect upon either eye. The near (accommodation) reflex is not abolished. Blindness due to destruction of both optic nerves results in the loss of the reflexes for light as well as of those for accommodation. (b) Hemianopia due to a lesion of the chiasma, or

of the optic tract, results in the loss of both the direct and indirect reactions to light thrown upon the blind half of either retina. Light falling upon the sound halves of the retinas causes the normal response. This is known as *Wernicke's hemianopic pupillary reaction*.⁵ (c) Loss of the light reflex (both direct and indirect reactions) with retention or even exaggeration of the accommodation-convergence reflex is known as the *Argyll-Robertson pupil*. The pupil is also, as a rule, smaller than normal (myosis) and does not dilate to a painful stimulus nor fully to atropinization; the vestibular reflex is frequently absent as well. The abnormal pupillary responses occur quite apart from any defect of vision. Though usually bilateral the Argyll-Robertson pupil is sometimes confined to one side. It is most commonly seen in syphilitic degeneration of the central nervous system (e.g., tabes), but occurs in other conditions as well. The site of the lesion responsible for the Argyll-Robertson pupil is not known precisely. Merritt and Moore give evidence for placing it in the region of the posterior commissure where presumably, the neighboring dilator pathway is also interrupted. Scala and Spiegel believe from the results of their experiments that the disease involves the synapses between the afferent and efferent neurons of the light reflex, that is, in the oculomotor nucleus itself. (d) Destruction of the oculomotor nucleus or of the efferent pathway abolishes all light and accommodation reactions on the same side. The direct and indirect reactions are retained on the contralateral side. (e) Lesions involving the visual pathway after the separation of the visual and pupillary fibers, e.g., geniculate body, optic radiations or occipital cortex, leave the light reflex unaffected. (f) A bilateral lesion implicating the pathway from the cortex to the center for accommodation in the oculo-motor nucleus will cause a loss of the near reflex and leave the light reflexes intact. This is the converse of the Argyll-Robertson pupil.

The effects of drugs upon the pupil and ciliary muscle

Dilatation of the pupil is spoken of as *mydriasis*; constriction as *miosis*. Drugs which cause pupillary dilatation are therefore called *mydriatics*; those which cause constriction, *miotics*. Paralysis of the ciliary muscles is known as *cycloplegia*; drugs which cause this effect are called *cycloplegics*.

⁵ Owing to the difficulty of confining a beam of light to the blind half of the retina it is not an easy matter to demonstrate this reaction.

Mydriasis is caused by drugs which:

- (a) Paralyze the peripheral constrictor (parasympathetic) mechanism, such as atropine, or homatropine. Atropine is also cycloplegic, homatropine much less so.
- (b) Stimulate the dilator (sympathetic) mechanism, e.g., adrenaline, cocaine. These drugs have no effect upon accommodation.

Miosis is caused by drugs which:

- (a) Stimulate the peripheral constrictor mechanism, e.g., pilocarpine, physostigmine, muscarine. These drugs also cause spasm of the ciliary muscles.
- (b) Diminish the inhibition of the constrictor center, e.g., morphine. The action of this drug upon the pupil depends largely upon the intensity of the illumination. It appears, therefore, to exert its effect, mainly, by increasing the sensitivity of the light reflex.
- (c) Stimulate the constrictor center, e.g., picrotoxin.

Corresponding retinal points

When the gaze is directed to an object, an image is formed by each eye and impulses are conveyed to both sides of the brain, yet perfect fusion of the two images occurs in consciousness and only one image is seen. This characteristic of *binocular vision* is explained upon the theory of *corresponding retinal points*. The corresponding points in the retinas (foveas) which when stimulated simultaneously cause a single visual sensation, lie in the nasal half of one retina and the temporal half of the other. When the eyes are converged, the retinas are turned so that the images fall upon these corresponding parts. If, as a result of unequal action of the ocular muscles, this cannot be brought about, the separate images are not fused in consciousness and an object appears double. This abnormality of vision is known as *diplopia*.

The horopter. When the eyes are fixed upon any point in space, a number of other points can be located by calculation which are projected upon corresponding points of the two retinas (foveas). A line joining such points forms a circle called the *horopter* which passes through the fixation point and the nodal points of the eyes. The horopter will vary of course with the point of fixation of the eyes and does not exist unless the eye acts symmetrically (See Fig. 469). Points in the visual field lying outside the horopter do not fall on the corresponding points in the two retinas (peripheral retinas) and, as a consequence, actually cause a double impression. But this *physiological diplopia* as it is called does not thrust itself upon consciousness; it is suppressed or ignored and therefore does not cause confusion. Yet one can easily

demonstrate for himself that it exists. For example, when the eyes are fixated upon a near object, such as a pencil tip held close to the face, a more distant object may, through a conscious effort, be observed in duplicate.

STEREOSCOPIC VISION (GR. STEREOS, SOLID SKOPEO, 1 VIEW)

Our visual judgment of solidity, that is, our recognition that the object has depth as well as height and width, is due largely to the fact that corresponding points in the two retinas receive slightly dissimilar images of any given object. If the reader will look at some object in front of him, first closing one eye and then the other, he will find that the view seen by the right eye is slightly different from that seen by the left. The right eye is able to see more of the right side of the object, the left eye more of the left side. The two slightly disparate images are fused in the brain, yet the composite image has hidden within it something of each separate one; upon this the stereoscopic effect depends. The fusion of the dissimilar images by the brain, and the impression of depth and solidity produced thereby, lies in a field of psychology of which little is known.

The instrument known as a stereoscope produces an illusion of solidity by making use of the principle of simultaneous stimulation of the retinas by dissimilar images. A photograph taken with an ordinary camera appears flat because identical images are formed upon the retinas. A stereoscopic photograph, on the other hand, is taken by a camera provided with two lenses which are set, like the eyes, a short distance apart. Thus two slightly dissimilar views are taken which, when looked at through the stereoscope, are projected by means of prisms, one to each eye, so as to fall on corresponding retinal points. Steroscopic perception cannot, however, be explained entirely upon the basis of dissimilar retinal images, for though the discrimination of depth (or distance) is much more acute in binocular vision it is not abolished when one eye is closed. For example, when two objects are placed one in front of the other and viewed binocularly from a distance of about 6 meters the least distance between them which can be perceived by the average normal eyes is around 20 mm. When one eye is covered the least perceptible difference is increased to 120 mm. The other factors concerned in depth perception are as follows.

(1) *The apparent size of various objects in our field of vision.* We know from experience the approximate dimensions of the objects which we see, but the image which an object casts upon the fovea diminishes as its distance increases (p. 961). For example, a church steeple at a distance casts an image upon the retina no larger, perhaps smaller, than would a pencil held a few inches from the eyes. We know the relative sizes of the two objects, and therefore infer that the steeple must be far away and the pencil near.

(2) *The apparent change in color of an object with distance.* The atmosphere is not perfectly transparent or equally so for all wave lengths. Tree-clad hills, which we know to be green, appear bluish in the distance; the colors of many other objects appear to fade with distance, their detail and outline being dimmed by haze.

(3) *The blocking out of parts of a distant view by objects between it and the eyes* gives a sensation of depth.

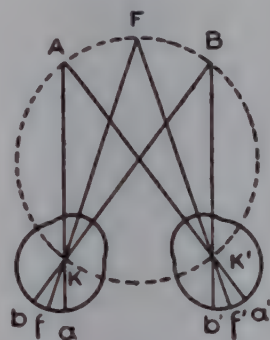


FIG. 469. The horopter (Müller). F is the fixation point. The images of A, F, and B fall upon the retinae at corresponding points as aa' , ff' , and bb' . The projection of all such corresponding points lies upon the circumference of the dotted circle. It is obvious that there is a different horopter for each position of F. (After Duke-Elder, *Text Book of Ophthalmology*.)

(4) *Mathematical perspective.* Straight lines running into the distance which are actually parallel (or objects along imaginary straight lines) are convergent in the retinal image. When we look down a railway track, for example, the rails appear to converge towards some point beyond the horizon. This arrangement of lines in the retinal image we have come to associate with distance. The artist draws objects along imaginary lines which run towards a point in the background of his picture.

(5) *Parallax.* When one moves in any direction, near objects appear to move in the opposite direction, those in the background in the same direction as ourselves. This apparent movement of near objects in relation to ones farther away is called parallax; it is also produced by a movement of the head or eyes, even though the body remains stationary. Now, involuntary movements of the eyes are continually taking place with the production of parallax; this is believed to be an important but not an essential factor in giving us a sense of depth. That it is not an essential factor in depth

perception was proved by Dove (1841) who found that objects illuminated by an electric spark were seen in three dimensions; the stereoscopic effect, as was shown later by Volkmann, is experienced, though the duration of the flash is only 0.000,001 second.

(6) *The distribution of light and shade over the surface of an object and the shadow which it casts upon its surroundings* is also an important factor in the production of the stereoscopic effect.

Normally, the images formed by the two eyes are very nearly equal in size, varying by less than one per cent. When they differ in size to a degree which prevents perfect fusion with a consequent impairment of binocular vision the condition is spoken of as *aniseikonia*. Little interference with binocular vision results unless the inequality of the images is more than four or five per cent. Aniseikonia may be a factor, according to Bielschowsky, in the production of strabismus.

OCULAR MOVEMENTS

The innervation of the ocular muscles

The nerves supplying the extrinsic muscles of the eye are the 3rd (oculomotor), 4th (trochlear) and the 6th (abducent). The oculomotor nerve supplies all the extrinsic muscles of the eyeball except the superior oblique and the external rectus. It also supplies the striated portion of the levator palpebrae superioris and conveys parasympathetic fibers to the sphincter pupillae (p. 1012) and ciliary muscle. The deep smooth muscle component of the elevator of the lid is innervated by the sympathetic (p. 1013).

THE NUCLEUS OF THE 3RD NERVE is situated in the floor of the Sylvian (cerebral) aqueduct and subjacent to the superior colliculus. It is in close relation to the medial longitudinal fasciculus (p. 857). It is composed of a group of five smaller nuclei (fig. 470).

(a) The *central nucleus* (Perlia's nucleus) fuses with its fellow of the opposite side to form a single gray mass in the mid-line. It is probably the center for convergence of the eyes (internal recti). (b) The *caudal central nucleus* lies in line with and behind the former. It also fuses with its fellow of the opposite side. Functionally it is considered a part of the central nucleus and is shown by Brouwer and others as actually continuous with the latter. (c) The *dorsi-lateral nucleus*. It and the next two nuclei are paired. The dorsi-lateral nucleus is probably the center for upward movements of the eyes (superior rectus and inferior oblique muscles). The *striped muscle* of the levator palpebrae superioris also, it is believed, receives its innervation from this nucleus. (d) The *ventrimedial nucleus*, lying medial, ventral and caudad to the preceding is thought to be concerned with downward movements (inferior rectus). (e) The *Edinger-Westphal nucleus* lies on each side dorsal and lateral to the central nucleus.

It is believed to supply fibers to the sphincter pupillae and ciliary muscle.

The axons arising from these cell groups pass for most part into the nerve of the same side. A few fibers supplying the internal and inferior recti and inferior oblique muscles decussate with those of the opposite side.

The fibers after issuing from the oculomotor nucleus form a well-defined tract (tract of the oculomotor nerve) which runs downwards and forwards through the tegmentum, traversing the red nucleus and mesencephalic portion of the substantia nigra. They emerge from the medial aspect of the cerebral peduncle.

THE NUCLEUS OF THE TROCHLEAR NERVE lies on the floor of the cerebral aqueduct adjacent to the posterior end of the ventri-medial nucleus of the oculomotor nerve, and on a level with the inferior colliculus. It supplies the superior oblique, and, with the ventrimedial part of the oculomotor nucleus, forms a center for downward movements of the eye. The fibers arising from the trochlear nucleus differ from those of any other cranial nerve in that the great majority decussate with those of the opposite side. After leaving the nucleus the fibers curve dorsally around the central gray mass surrounding the aqueduct to reach the anterior medullary velum in which the decussation occurs. They emerge from the dorsal surface of the anterior medullary velum on one side of its frenulum and immediately behind the inferior colliculus.

THE ABDUCENT NUCLEUS furnishes fibers to the external rectus. It lies in the pons close to the median line and subjacent to the upper part of the floor of the 4th ventricle. Its fibers pass downwards and forwards through the pons to emerge without crossing at the latter's lower border. The fibers of the facial nerve loop around the abducent nucleus (p. 860).

The nuclei of the three ocular nerves receive fibers from: (a) the pyramidal tract of the opposite side, (b) the medial longitudinal fasciculus through which the three nuclei are connected with one another, with the vestibular nucleus, with the spinal cord and probably with the facial nucleus. It has been suggested that fibers from the oculomotor nucleus may enter the lateral nucleus and be then conveyed in the facial to the orbicularis oculi and the corrugator supercilii. The tectobulbar tract which relays to the three nuclei impulses entering the superior colliculus from the optic tract and the visual cortex.

The eyes are said to be in a *position of rest* in their *primary position* when their direction is maintained simply by the tone of the ocular muscles, that is, when the gaze is straight ahead and far away and not directed to any particular point in space. The visual axes are then parallel. When the eyes view some definite object they are turned by the contraction of the ocular muscles and converged so that the visual axes meet at the

erved object and an image of the object falls upon a corresponding point on each macula (p. 1014). The closer the object to the eye the greater the degree of convergence (p. 997). This movement of the eyes for the acute observation of an object is called *fixation*. The point where the visual axes meet is called the *fixation point* and the lines joining the latter to the fovea, i.e., the central axes, are sometimes called the *fixation lines*. The widest limits of vision in all directions within which eyes can fixate is called the *field of vision*. When surveyed by means of the perimeter it is found to be nearly circular with a diameter about 100° . Its boundaries therefore lie well within the limits of the binocular visual field (1006).

The eyeball is rotated in its socket (formed by the *orbita bulbi*) by the ocular muscles around one or other of three *primary axes* which intersect one another at right angles near the center of the globe. One axis is vertical, around it lateral movements (adduction and abduction) take place, i.e., in the horizontal plane. Another runs from before backwards and coincides with the visual axis; movements in the frontal plane (torsion or wheel movements) take place around it. The third is transverse, it is the axis of rotation for upward and downward movements, i.e., movements in the sagittal plane. Though the movements of the eyeball are essentially and for practical purposes rotary in character, a very slight translatory movement may take place as a result of movements of the lids and variations in the width of the palpebral fissure, closure and opening of the lids causing a displacement backward and outward, and forward and inward, respectively. A slight displacement at right angles to the rotary movement also takes place during contractions of the ocular muscles, the eyeball therefore executing what has been described by Berlin as a screw movement. For this reason the center of rotation of the eyeball is not an absolutely fixed point but varies slightly. For general purposes, however, it may be taken as the point of intersection of the primary axes. This point is on the visual axis about 13 mm. from the anterior surface of the cornea.

In table 79 the actions of the individual ocular muscles are given, but no normal movement is effected out by one of these muscles alone. Thus, when the eye is abducted, the external rectus and the two obliques act in unison to turn the eye inwards. The depressor and elevator components in the actions of the respective oblique muscles cancel one another. Similarly, adduction effected by contraction of the internal rectus is balanced by the superior and inferior recti. Again,

the depressor and elevating actions of the latter two muscles neutralize one another. In looking upwards the eye is elevated by the combined action of the superior rectus and the inferior oblique. In looking downwards the inferior rectus and the superior oblique act together, the subsidiary action of the inferior rectus in turning the eye inwards being offset by the opposite action of the superior oblique. This compound action of the ocular muscles makes for smooth and steady movement and rapid fixation of the eyeball. It will be seen from figure 471 that the obliques and the superior and inferior recti when contracting individually produce a rotary or wheel-like movement. When acting in pairs the rotary actions being in opposite



FIG. 470. A scheme of the various groups of cells which together constitute the nucleus of the oculomotor nerve. A, the dorsolateral nucleus; B, the ventrimedial nucleus; C, the central nucleus; D, the Edinger-Westphal nucleus; E, the caudal central nucleus; m, the third ventricle (from Gray, *Anatomy of the Human Body*, after le Gros Clark).

directions antagonize one another so that normally no such movement occurs. It has been stated by Hering that every central influence governing eye movements, excitatory or inhibitory, reaches both eyes equally (Hering's law) causing contraction or relaxation of associated muscle groups.

The actions of the eye muscles follow the principle of reciprocal innervation. Thus, when the eye is turned outwards the external rectus and the two obliques contract while their antagonists (inferior, external and superior recti) are inhibited. The two eyes act in unison, both turning in the same direction—*conjugate deviation*—and reciprocal innervation is extended to include muscle groups in the two eyes, thus indicating their control from a single center. Thus, stimulation of the posterior part of the 2nd frontal convolution causes conjugate deviation of the eyes to the opposite side. This involves contraction of the abductors and inhibi-

tion of the adductors of one eye and converse actions in the opposite eye (i.e., inhibition of the abductors accompanied by contraction of the adductors). Destruction of the cortical area results in the loss of the conjugate movement without paralysis of the individual

action of the affected muscle. (b) *Paralytic strabismus or squint*. When an effort is made to turn the eyes in the direction of the paralyzed muscle, the affected eye remains stationary or makes a smaller movement than does the sound eye. That is, it deviates in relation to the latter in a direction opposite to that of the normal action of the paralyzed muscle. The visual axes, therefore, do not bear their normal relationship to one another. This is called the *primary deviation*. If a screen is placed in front of the sound eye while an attempt is made to fixate the affected eye upon an object situated towards the side of the paralyzed muscle, the sound eye deviates in the direction of action of the latter. This *secondary deviation*, as it is termed, is greater than the primary deviation of the paralyzed eye. The greater deviation of the sound eye is attributed to the unusual effort exerted in the attempt to fixate the paralyzed eye, an unnecessarily strong motor discharge being transmitted simultaneously to the muscle of the sound eye which normally acts conjointly (conjugate deviation) with the paralyzed muscle.

(c) *Diplopia; false projection of the visual field*. It is as a result of weakness or paralysis of the muscles of

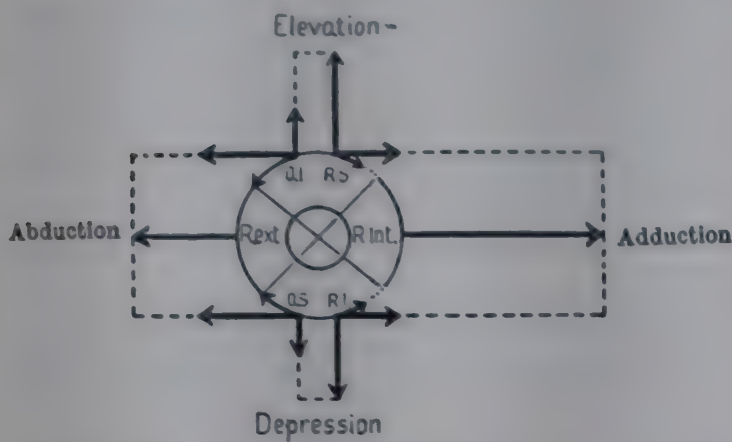


FIG. 471. Diagram to illustrate the actions of the ocular muscles. O.I., inferior oblique; RS, superior rectus; R ext, external rectus; R int, internal rectus; O.S., superior oblique; RI, inferior rectus (from Fuchs after Marquez).

TABLE 79

MUSCLE		MOVEMENT	INNERVATION	DIPLOPIA DUE TO OCULAR PARALYSIS POSITION OF FALSE IMAGE IN RELATION TO TRUE WHEN RIGHT EYE AFFECTED (APPLICABLE TO LEFT EYE IF RIGHT BE CHANGED TO LEFT AND VICE VERSA)
Rectus	Superior	Adductor and elevator	Oculomotor	Above, to left of and tilted away from true image (crossed diplopia)
	Inferior	Adductor and depressor	Oculomotor	Below, to left and tilted towards true image (crossed diplopia)
	Internal	Adductor	Oculomotor	Level with, parallel to and on the left of true image (crossed diplopia)
	External	Abductor	Abducens	Level with, parallel to and on the right of true image
Oblique	Inferior	Abductor and elevator	Oculomotor	Above, to right of and tilted away from true image
	Superior	Abductor and depressor	Trochlear	Below, to right of and tilted toward true image
Levator palp. sup.		Elevator of eyelid antagonizes the action of the palpebral part of the orbicularis oculi	Oculomotor	

muscles. The act of *convergence*, in which both eyes are adducted, is due to the conjoint contraction of the internal recti. The center for this movement is probably in the central nucleus of the oculomotor nerve. A higher center for the movement is also situated in the frontal cortex.

The effects upon the eye movements of paralysis or weakness (*paresis*) of the ocular muscles. (a) *Limitation of movement* of the eye in the direction of the normal

one eye, or of an imbalance from whatever cause occurs between the actions of the ocular muscles of the two eyes, the images do not fall upon corresponding retinal points and *diplopia* or *double vision* results. The image seen by the sound eye is called the *true image*, that seen by the affected eye is called the *false image*. The false image lies to one side, above or below the true image, depending upon the ocular muscle which is paralyzed. In the case of the oblique muscles and the superior

and inferior recti, the false image lies above or below the true image—a little to one or other side and tilted towards or away from it (see table 79, p. 1018). The false image is always displaced in the direction of the normal action of the paralyzed muscle. Thus, in paralysis of the right external rectus the right eye is not turned outwards when the subject attempts to look at an object towards his right side. The image of the object falls upon the temporal half of the left macula and is therefore projected into the nasal half of the visual field of that eye. But, in the affected eye the image falls upon the nasal half of the retina and is therefore projected into the temporal half of the right visual field. The image seen by the right eye (false image) therefore lies to the right of that seen by the left (true image). When the false image is on the same side of the true image as the affected eye the diplopia is said to be *simple* or *uncrossed*; if it lies on the opposite side of the true image the diplopia is said to be *crossed*.

If in a case of diplopia the sound eye is covered and the patient asked to turn his eyes, and to touch quickly an object placed to one side of his line of vision, but in the direction of the paralyzed muscle, he places his hand some distance from the object's true position. Normally, information concerning the positions of objects in space is to a large extent dependent upon

proprioceptor impulses arising in the ocular muscles. When, for example, we look at an object straight in front of us an image falls upon the macula of each retina. When we look at an object to one side the eyes are turned so that the images fall again upon precisely the same areas—the maculae. The actual position of the object—whether in front or to one side—is made known to us by afferent impulses set up in the muscles as they turn the eyes into position. Such impulses serve also as a basis for the nice correlation between visual sensations and various body movements. When, as a result of paralysis of certain muscles, the eye does not move with the sound eye, the impulses arising in the muscles of the latter convey the impression, nevertheless, that such a movement has taken place. Let us say the outward movement of the right eye is paralyzed and the left, sound eye, is covered; when the latter turns to the right the patient believes the paralyzed eye does so to the same degree. The image in this eye, which continues to look forward, falls upon the nasal side of the retina. Since earliest experiences have taught him that an image falling upon the nasal part of the retina when this eye is rotated outwards represents an object well over to the right, he falsely projects the image into this position, and makes the appropriate movement of the hand in an attempt to touch the object.

CHAPTER LXXVIII

THE EAR. ANATOMICAL OUTLINE. SOUND GENERAL PRINCIPLES

ANATOMICAL OUTLINE

In order that the reader may follow with the least effort the account of the physiological mechanisms of hearing, the anatomy of the auditory apparatus and especially those features having a direct bearing upon function will be briefly described. For a more detailed description reference should be made to any standard text on anatomy.

The external ear comprises the cutaneous and cartilaginous appendage known as the *auricle* or *pinna*, and the short passage—the *external auditory meatus* leading into and penetrating the temporal bone (fig. 472).

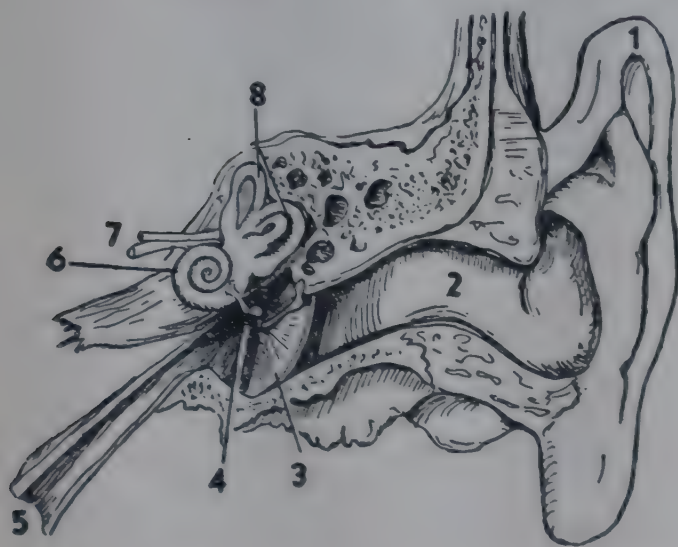


FIG. 472. Plan of the ear. (Redrawn and modified from Arnold.) 1, the auricle (or pinna); 2, external auditory canal (or meatus); 3, the tympanic membrane (sectioned); 4, the tympanic cavity (middle ear), the chain of ossicles lies just above the pointer; 5, Eustachian tube; 6, cochlea; 7, acoustic nerve, showing cochlear and vestibular divisions; 8, semicircular canals.

The external auditory meatus is an S shaped canal, being directed inwards, upwards and forwards, then, upwards and backwards and finally, forwards and slightly downwards to end blindly at the drum membrane. The inner 16 mm. or so of the canal (*pars ossea*) forms a tunnel in the temporal bone. The wall of the outer 8 millimeters of the meatus is composed of cartilage (*pars cartilaginea*); the entire canal, including its inner blind end formed by the drum membrane, is lined by skin.

The middle ear, *tympanic cavity* or *drum* is a chamber measuring about $15 \times 5 \times 2$ mm. and situated within the petrous bone. It is lined by mucous membrane. Except over the tympanic membrane and part of the inner wall, the epithelium is ciliated. The outer wall

of the tympanic cavity is formed mainly by the flexible *tympanic (drum) membrane*, while its inner wall which separates it from the internal ear is composed of bone except for the *oval* and *round windows* (*fenestra vestibuli* and *fenestra cochleae*). The inner wall presents a rounded eminence—the *promontory*—caused by the projection laterally of the basal turn of the cochlea. The oval window lies above the posterior part of the promontory. The round window which is closed by a delicate membrane is situated at the bottom of a deep hollow or niche lying just below this end of the promontory. The oval window lodges the footplate of the stapes. The tympanic cavity is filled with air which is maintained at atmospheric pressure by means of the *Eustachian tube (auditory tube)* which runs from the lower part of its anterior wall to the nasopharynx. The lower opening of this tube is closed at ordinary times but is dilated during swallowing by contraction of the *salpingopharyngeus* and *dilator tubae* muscles (see p. 1044).

The tympanic membrane is elliptical, measuring about 10 mm. in height and 9 mm. in width. It is placed obliquely, being directed from above downwards and forwards to form an angle of 55° with the anterior and inferior walls of the external auditory meatus. It possesses three layers, the outermost being of skin and the innermost of non-ciliated mucous membrane. The middle layer or *membrana propria* is composed of two sets of fibers—a radial and a circular—arranged somewhat like the threads of a spider's web. The drum membrane is drawn inwards at the center and along the attachment of the handle of the malleus; its lateral surface is therefore concave, its medial surface convex. The point of greatest concavity, which corresponds with the tip of the handle of the malleus, is called the *umbo* (fig. 473).

The drum membrane is observed during life by means of a light thrown into the meatus through an aural speculum. The healthy membrane viewed in this way is pearl gray in color, pinkish or faintly yellow. Above and anteriorly near its circumference the membrane presents a small white spot caused by the projection of the lateral process of the malleus; from this point a faint ridge corresponding with the handle of the malleus extends to the umbo. Two faint folds—the *anterior* and *posterior malleolar folds*—extend forward and backward, respectively, from the lateral process of the malleus, enclosing a small triangular area. The part of the tympanic membrane within this area is thin and lax; it is known as *Shrapnell's membrane* or the *pars flaccida*. The rest of the drum membrane is tight and

glistening (*pars tensa*). The lustre of the membrane gives rise to a bright triangular area, the "cone of light." This is situated with its apex at the umbo and its base directed downwards and forwards. For convenience in describing the position of a lesion of the drum membrane it is mapped out into quadrants by a line represented by the handle of the malleus and its continuation downwards and by another passing through the umbo at right angles to the first.

Three miniature bones—the *auditory ossicles*—jointed together stretch across the tympanic cavity from the drum membrane to the oval window (fig. 474). These are named, somewhat imaginatively from their shapes, the malleus (hammer), the incus (anvil) and the stapes (stirrup). The *malleus* (8–9 mm. long) consists of a handle (or manubrium) which is attached along the upper half of the vertical diameter of the tympanic membrane, a head (or capitellum) and two processes, a lateral and an anterior. The *incus* is shaped like a premolar tooth; the anterior surface of its body presents a saddle-shaped facet which articulates

attached to the malleus—the *anterior, superior and lateral ligaments of the malleus*; a fourth connects the short process of the incus to the posterior wall of the tympanum; the fifth is the annular ligament of the stapes just mentioned.

The tympanum contains two minute muscles—the *tensor tympani* and the *stapedius*. The former arises from the roof of the cartilaginous part of the Eustachian tube and from the adjacent part of the great wing of the sphenoid bone; its tendon turns laterally to be inserted into the medial edge and anterior surface of the handle of the malleus (fig. 474). When it contracts it pulls the handle of the malleus inwards, thereby preventing excessive displacement outwards of the tympanic membrane. The stapedius takes its origin from within an eminence (*eminencia pyramidalis*) on the posterior tympanic wall and passing forwards is inserted into the posterior surface of the neck of the stapes; its action pulls the head of the ossicle backwards, thus tilting the anterior edge of the base outwards, i.e., towards the tympanic cavity, and reducing the pressure

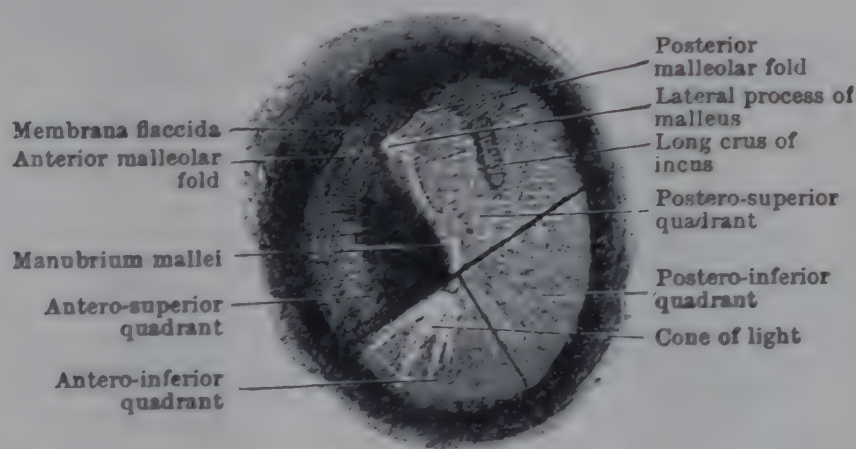


FIG. 473. Left tympanic membrane (as viewed from the external acoustic meatus). (From Cunningham's anatomy.)

with the posterior aspect of the head of the malleus. The lower part of the articular facet is hollowed out for the reception of the prominent inferior margin of the facet on the posterior surface of the head of the malleus—the so-called *spur* or *cog-tooth* of the malleus. The incus has a long and a short process; the former projects downwards and, turning inwards at the tip, connects through a ball and socket joint with the head of the stapes. The *stapes* shows a base (footplate of the stirrup) and two curved crura which join laterally to form an arch; a rounded eminence called the head arises from the center of the latter. The slight constriction between the head and the junction of the crura is called the neck. The head of the stapes, as just mentioned, articulates with the incus. The base fits into the oval window and is coated with cartilage which is connected around its circumference to the margins of the oval window by a ring of elastic fibers, known as the *annular ligament*.

The auditory ossicles are connected to the walls of the tympanum by five ligaments. Three of these are

upon the perilymph. These muscles are under reflex control, contracting to sound stimuli over the entire range of audible frequencies. The thresholds for these reflexes are lowest for tones of from 2000 to 4000 c.p.s. (rabbit). A sound in one ear causes increased tone of the tensor tympani of the opposite ear. This muscle also contracts during yawning. The tensor tympani is supplied by the fifth nerve, the stapedius by the seventh.

Two main views have been expressed concerning the functions of the intra-aural muscles. Some believe that they are *protective* in action, their contractions tending to reduce the amplitude of the vibrations of the tympanic membrane and ossicles particularly to low tones, thus protecting the delicate structures of the internal ear from injury. The other view, generally referred to as the *accommodative theory*, holds that the stapedius and tensor tympani act to "tune up" the transmitting mechanism of the middle ear and thus to increase its sensitivity to any given vibration frequency. It has been shown, however, by H. Wiggers in the

guinea pig that the transmissibility of low tones (below 1000 cycles) to the internal ear is *reduced* by contraction of the stapedius and tensor tympani; the transmission of medium tones (1300 to 1800 cycles) is slightly enhanced while that of high tones (over 2000 cycles) is unaffected. In the human subject the transmission of tones within the range of a conversational voice and of all other tones of low pitch is reduced. These observations indicate that the function of the intra-aural muscles is mainly protective; any direct effect upon

are at its apex or *cupula* which is directed forwards and laterally, the largest turns at the base which look backwards and inwards and forms part of the outer wall of the *internal auditory meatus*. A ledge of bone (*lamina spiralis ossea*) winding around the modiolus like the thread of a screw-nail divides the spiral canal incompletely into two parts. The partition is completed by a membranous structure—the *basilar membrane*—which extends from the tip of the lamina spiralis ossea to the outer wall of the canal (see fig. 475). A second membrane—*Reissner's membrane*—stretches from the upper surface of the bony lamina to a point a short distance above the outer attachment of the basilar

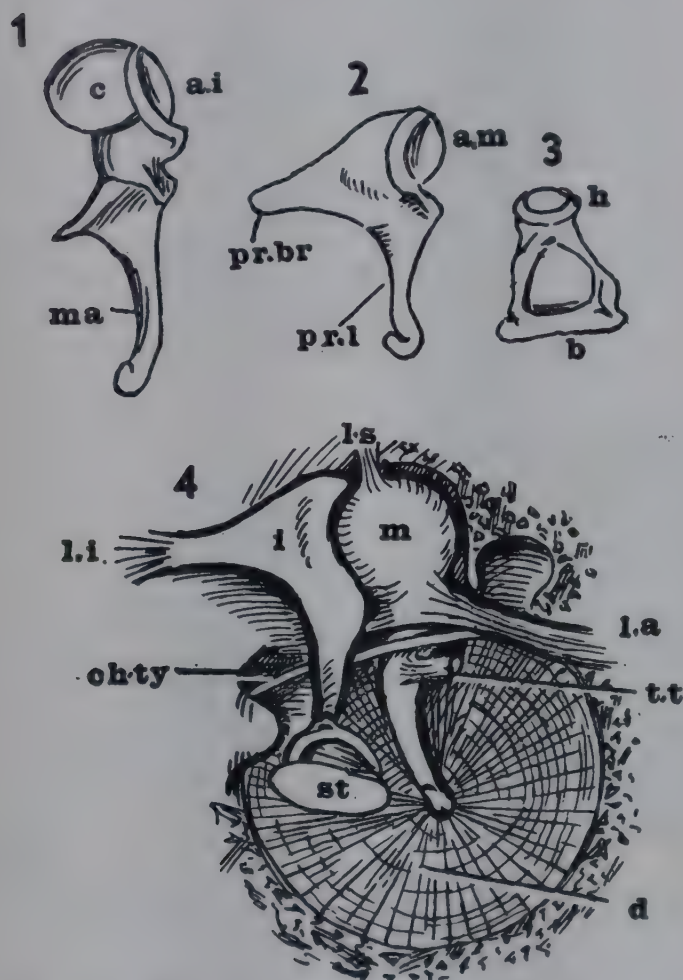


FIG. 474. The auditory ossicles. 1, left malleus viewed from outer side, c, head, a.i, articular surface for incus; ma, handle. 2, left incus, pr.br, short process; pr.l, long process which articulates with stapes; a.m. articular surface for malleus. 3, left stapes, h, head; b, base or "footplate"; 4, the middle ear viewed from the inner aspect and showing ossicles in position; d, drum membrane; i, incus; m, malleus; st, stapes; ch.ty, chorda tympani nerve; l.s., ligament of malleus; l.i, ligament of incus; t.t, tendon of tensor tympani muscle.

auditory acuity is limited to a small pitch range. However, their action in reducing the efficiency of the transmission system for low tones may indirectly, by diminishing the masking effect (p. 1031) of such tones, increase the acuity for higher frequencies.

The *internal ear* or *labyrinth*, situated within the temporal bone on the inner side of the middle ear, contains the auditory sense organs. The latter lie within a spiral canal called the *cochlea* (L. a *snail's shell*). The canal makes $2\frac{1}{2}$ turns round a central pillar of bone called the *modiolus*. The smallest turns of the cochlea

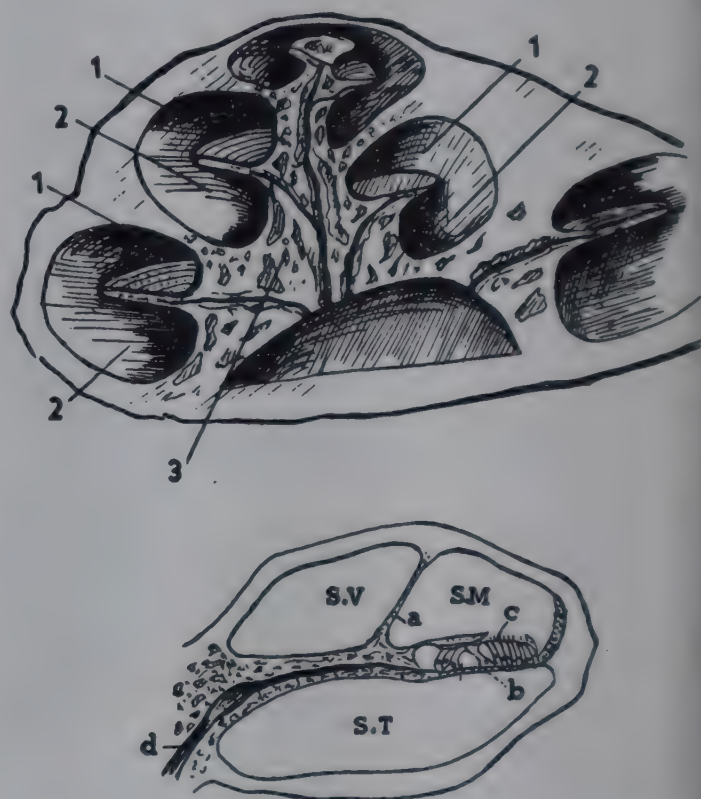


FIG. 475. Upper, a view of the osseous cochlea divided through the middle. 1, scala vestibuli; 2, scala tympani; 3, modiolus, showing tunnels transmitting branches of auditory nerve. Lower, enlarged sketch of one turn of the cochlea (redrawn after Quain) S.V, scala vestibuli; S.M, scala media (cochlear duct); S.T, scala tympani; a, Reissner's membrane; b, basilar membrane; c, organ of Corti; d, auditory nerve.

membrane. The original osseous canal is divided in this way into three spiral compartments or galleries. The gallery below the basilar membrane is called the *scala tympani*, the one above Reissner's membrane, the *scala vestibuli*, while the one enclosed between the two membranes is known as the *scala media*, the *cochlear duct* or the *membranous cochlea*. The membranous cochlea is filled with a fluid known as *endolymph*, while the osseous canals, i.e., the *scala vestibuli* and *scala tympani*, are filled with *perilymph*. The *scala vestibuli* and *scala tympani* communicate with one another at the cupula of the cochlea through a small aperture called the *helicotrema*. The *scala media* ends here as a closed sac, but its basal extremity communicates with the non-auditory labyrinth through the *canalis reuniens* or *duct of Hensen* (p. 836). The *perilymph* and *endo-*

lymph have different origins. The former is actually cerebrospinal fluid, the osseous canals communicating with the subarachnoid space through the *ductus perilymphaticus* which passes from the floor of the vestibule to the posterior fossa of the skull. The origin of the endolymph is unknown; it is possibly a secretion or transudate furnished by the stria vascularis. The scala vestibuli opens out near the central part of the labyrinth into an ovoid osseous chamber (6 x 4 x 4 mm.) called the *vestibule*. This chamber contains the utricle and saccule; the osseous semicircular canals open into its posterior part (p. 835). Its lateral wall separates it from the middle ear and contains the oval window.

The auditory receptors. The sensory cells, together with sustentacular elements constitute a structure known as the *spiral organ of Corti* (fig. 476). This lies within the scala media, occupying the inner half or so of the basilar membrane. It presents towards its inner part two rows of elongated epithelial elements of peculiar shape—the *inner* and *outer rods* (or *pillars*) of

cells. The *outer* hair cells are longer than the inner and more numerous (12,000); they are separated from the basilar membrane by cells arranged in several rows—the *cells of Deiters*—which send slender processes between the rows of the sensitive cells. That part of the organ of Corti lying on the outer side of Deiters' cells and the outermost row of hair cells is composed of several layers of columnar cells—the *supporting cells of Hensen*.

The *tectorial membrane* is a delicate, almost homogeneous structure, somewhat paddle-shaped in transverse sections of the scala media; it overlies the inner half or more of the spiral organ. Arising from a point near the base of the lamina spiralis ossea it ends laterally in an irregularly fringed or scalloped free margin. The hairs of the sensory cells of all four rows are embedded in its under surface.

The structure of the basilar membrane. The inner part (*zona arcuata*) of the basilar membrane where it supports the spiral organ is thin; its outer thicker part (*zona pectinata*) is covered by a single layer of columnar

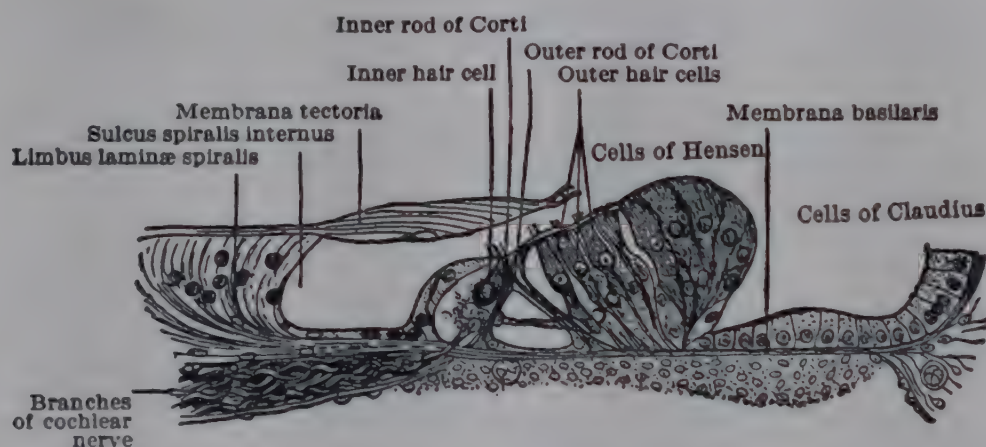


FIG. 476. Section across the organ of Corti. (After Retzius.)

Corti—which stand with their expanded bases planted upon the basilar membrane. The bases of the rods of the two rows are separated by an interval, but above the membrane their bodies incline towards one another and, meeting at an angle, their extremities fit into one another in a manner much as one clasps a fist with the other hand. They form by this arrangement a triangular tunnel whose floor is covered by two nucleated scraps of protoplasm which actually are the undifferentiated parts of the cells from which the corresponding rods have developed. The arches of Corti increase progressively in height from the basal to the apical turns of the cochlea.

The *hair cells* are the essential sensory elements. They are seen as four rows of short columnar cells, one row lying on the inner side and three on the outer side of the corresponding rod. The *inner* hair cells number about 3500; their free ends are in line with the surfaces of the rods, but their bases extend only half way to the basilar membrane. The free surface of each hair cell of both inner and outer rows is surmounted by some twenty hair-like processes. One or two rows of cells support the bases and inner aspects of the inner hair

cells named the *cells of Claudius*. The substantia propria of both zones of the membrane show numerous fibers—the *auditory strings*—embedded in a homogeneous ground substance. The strings in the outer zone are straight and smooth and run for the most part transversely; those of the inner zone are thinner and arranged in the form of a net. The total number of fibers in the human cochlea is 24,000, according to the generally accepted estimate of Retzius. The basilar membrane when uncoiled shows a gradual taper; it measures about 30 mm. in length in man. It is about three times wider at its apical than at its basal end. The auditory strings vary in length in a corresponding manner, being from 65 μ to 160 μ long at the base and from 350 μ to 500 μ at the cupula. The outer end of the basilar membrane is attached to the wall of the cochlear canal throughout its entire length by a ligamentous band called the *external spiral ligament*. This appears in sections of the canal as a conical structure composed of radiating fibers; it is relatively thick and strong in the basal turns but becomes progressively narrower in the direction of the cupula where it dwindles to a delicate strand.

The external spiral ligament is covered by cubical epithelium. Situated between the epithelial cells and the underlying fibrous tissue are numerous small blood vessels and capillary loops which together form a structure named the *stria vascularis*. The tissue surrounding the vessels contains pigment of varying amount depending upon the species. The *stria vascularis* is thought by some to have a secretory function.

Innervation of the hair cells. The cochlear division of the auditory (acoustic) nerve emerges as a number of fine filaments from the base of the modiolus in the internal auditory meatus. These are the central

of the 8th nerve after issuing from the internal auditory meatus, crosses the posterior fossa of the skull in close association with the vestibular division (p. 836) and the facial nerve. Reaching the lower border of the pons the cochlear fibers divide into two groups. The fibers of one group end around cells in the *ventral cochlear nucleus* situated upon the ventral aspect of the restiform body (fig. 477), those of the other group around cells of the *dorsal nucleus (tuberculum acousticum)* lying upon the dorso-lateral aspect of the restiform body. Secondary auditory neurons are situated in both these nuclei. The fibers issuing from

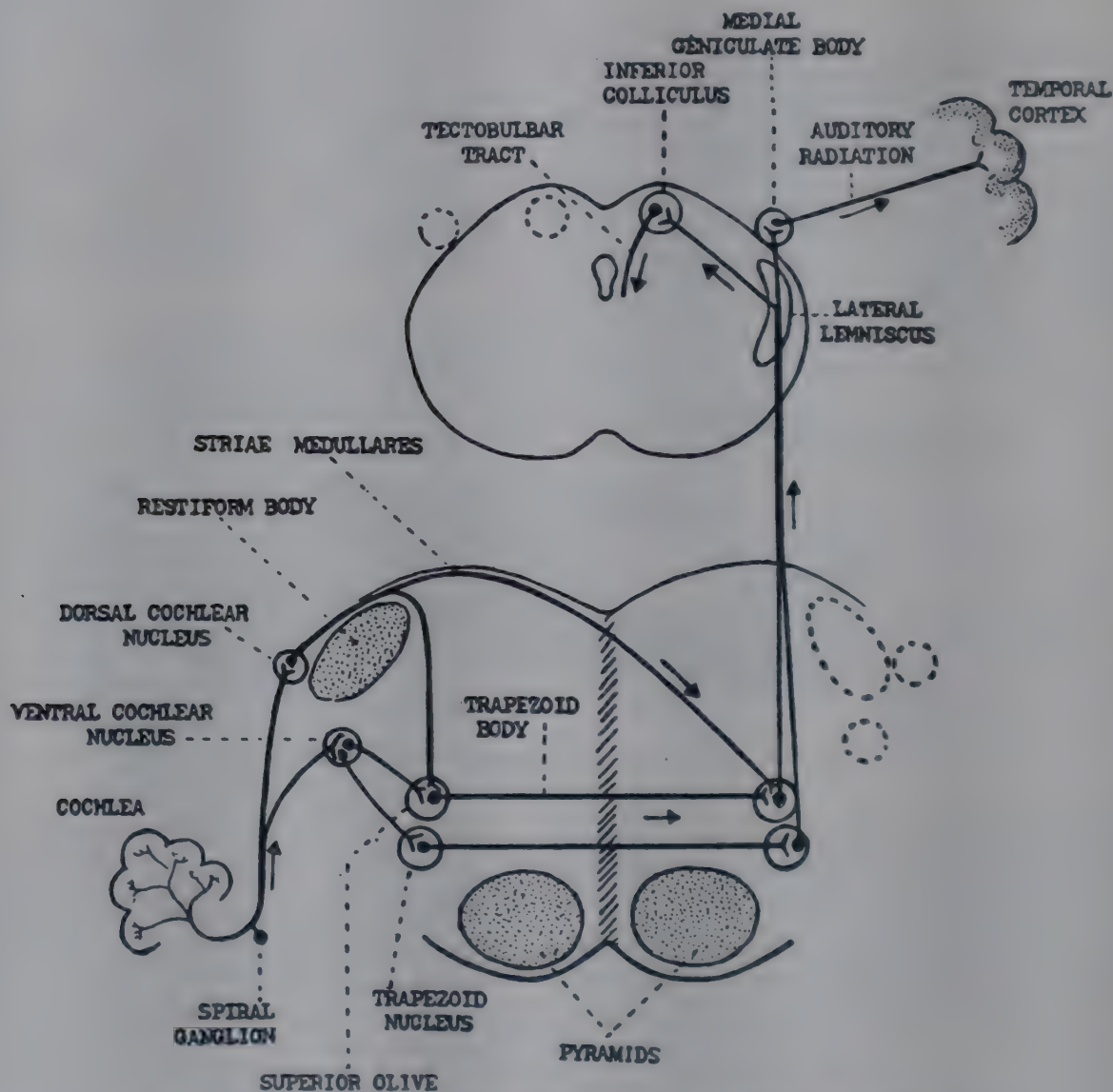


FIG. 477. Diagram of the auditory pathway (in part after Gray)

processes of the bipolar cells of the *spiral ganglion of the cochlea* which lies in the *spiral canal of the modiolus*; the latter twists through the bone along a line nearly corresponding with the origin of the lamina spiralis ossea. The peripheral processes (axons) of the bipolar cells proceed outwards in fine canals in the spiral lamina to its outer edge. The nerve filaments terminate as fine arborizations, some around the bases of the inner hair cells, others after crossing Corti's tunnel around the bases of the outer hair cells.

The non-auditory part of the labyrinth is described in Chapter LXVI.

THE AUDITORY PATHWAY. The cochlear division

the ventral nucleus pass medially, forming the trapezoid body and, crossing with those of the opposite side, ascend in the *lateral lemniscus*. (Some fibers from the ventral nucleus give off collaterals to the nucleus of the trapezoid body and of the superior olive; from these nuclei tertiary neurons convey impulses through the medial longitudinal fasciculus to the nuclei of the oculomotor, trochlear, abducens and spinal accessory nerves.) Fibers arising from the cells of the dorsal nucleus pass around the dorsal aspect of the restiform body, and proceed medially in the floor of the 4th ventricle, where they appear as well defined white strands—the *striae acousticae* (or *striae medullares*). Reaching the mid-

line they cross to the opposite side, and ascend with those of the ventral nucleus in the lateral lemniscus. Some fibers of the dorsal nucleus end in the nucleus of the superior olive, and some from both the dorsal and ventral nuclei join the lateral fillet of the same side. The lateral lemniscus as just indicated is composed of the secondary neurons of the auditory pathway and ascends in the reticular formation of the pons, its fibers ending in (a) the *substantia nigra*, (b) the *inferior colliculus* (corpus quadrigeminum), and (c) the *internal (medial) geniculate body*. Just as the superior colliculus serves as a center for visual reflexes, so the inferior colliculus is a center for auditory reflexes. It is not concerned with auditory sensations. It is connected by descending tracts with the nuclei of the brain stem and spinal centers (tectospinal tract). The internal geniculate body is the subcortical or primary auditory center.

The auditory radiation. The tertiary auditory neurons arise in the internal geniculate body, ascend in the posterior limb of the internal capsule external to the fibers of the optic radiation, and end in the cortex of the superior temporal convolution (Heschl's gyrus).

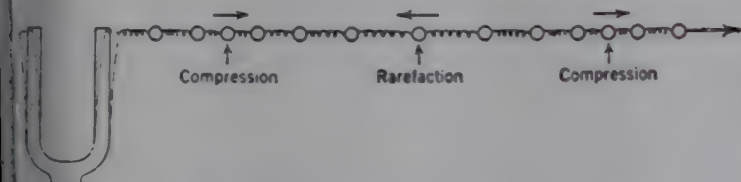


FIG. 478. Showing how one prong of a tuning fork compresses and rarefies the air. The circles represent little portions of air, while the springs are intended to show the elasticity of air. (After Watson, *Sound*.)

SOUND, GENERAL PRINCIPLES

All sound arises as a series of vibrations. The sound is transmitted through an elastic medium (e.g., air) as a train of alternating variations in pressure. For example, when the prongs of a tuning-fork are struck they vibrate, moving rapidly to and fro with a pendular motion and producing alternate compressions and decompressions (rarefactions) of the air in contact with their flat surfaces. The train of pressure alterations thus set up are transmitted through the air in all directions; reaching the drum membrane, they force it into vibration (fig. 478). The pendular movement of the tuning-fork is termed a *simple harmonic motion*. This movement is imparted to the air particles in contact with the prongs of the fork and through these to contiguous particles and so on through the medium. Simple harmonic motion may be illustrated by a mechanical model. In figure 478 the particles of air (O) are represented as connected by springs. When the prong of the fork moves outwards the first spring is compressed and a movement thereby transmitted to the attached particle.

The movement of the particle compresses the second spring and through it the corresponding particle, and so on through the series. The springs are not compressed all at the same instant but in succession, the movement of each particle occurring a little time after that of the particle immediately preceding. When the prong swings in the opposite direction the springs are stretched, the particles moving in reverse order, the movement showing a similar lag from particle to particle. Thus, the particles oscillate in a regular to and fro manner. Simple harmonic motion is defined as the *projection of a circular movement upon the diameter of the circle*. For example, if while a body is moving with constant velocity in a circle one observes it from a distance with the eye in the plane of the circle, it appears to oscillate back and forth like a shuttle along a straight line, that is, along the diameter of the circle. In order to indicate the location of the oscillating particle on its linear path at any instant, another particle,

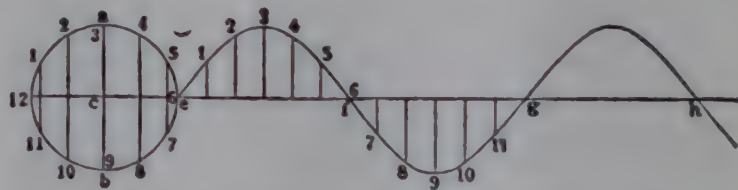


FIG. 479. Illustrating simple harmonic motion and circle of reference. (After Wilkinson and Gray.)

purely imaginary, is supposed to be traveling in a circle and always keeping vertically above the actual one. The orbit of this imaginary particle is called the *circle of reference* (see fig. 479). The distance which the particle travels from its equilibrium point (which is the center of its linear path), i.e., half a full excursion, will, of course, be proportional to the radius of the circle and gives the *amplitude* of the vibration. The position of the particle in the circle of reference is called the *phase* of its motion. A complete movement, i.e., from one phase to the next corresponding phase is termed a *cycle* or *double vibration* (d.v.) and the number of cycles per second (c.p.s.) is the *vibration frequency*. The distance from one particle to the next one in the same phase gives the wave length. The compression or stretching of a spring in the model corresponds to the movement of a particle of the medium in the same or in the opposite direction, respectively, to that in which the sound wave is moving; in their movement with the wave the air particles are closer together (compression), during the opposite movement they are further apart (rarefaction). Simple harmonic motion is

the commonest type of motion set up in air particles by vibrating bodies and *all musical tones are due to such motions or to a combination of them in different phases* (p. 1029).

Though, as stated above, sound is conducted as a series of compressions and expansions of the air, it is customary to represent it graphically as travelling like a series of water waves. But it must be pointed out that this is merely a useful convention derived from the fact that if we attach a writing point to a pendulum or tuning-fork executing simple harmonic motion, and have it inscribe its excursions upon a moving surface, a series of such waves will be drawn. Such a simple regular type of wave produced by a tuning-fork and shown in figure 479 is known as a sine wave, because when different points upon the wave are correlated with the positions of the moving particle on the circumference of the circle of reference, the ordinate at each point on the wave is proportional to the sine of the angle which the radius joining the particle on the circumference makes with the diameter of the circle. Simple or pure tones are all produced by waves of this type.

The *velocity of sound* varies with the elasticity of the medium and inversely with its density. Increased elasticity raises the velocity (the imaginary springs between the particles being stiffer respond more rapidly); greater density slows the rate of transmission owing to the greater inertia of the particles. The velocity of sound waves is about 1100 feet per second in air, 4,700 per second in water, 13,000 per second in wood and 16,500 in steel. The velocity of sound in a medium is obtained from the equation $v = \sqrt{E/d}$, in which E = elasticity and d = density. The wave length of a given tone is readily obtained by dividing its frequency of vibration (number of cycles per second) into the figure expressing its velocity. Thus the wave length of a sound transmitted through air and with a frequency of 550 cycles per second is $\left(\frac{1100}{550} = \right)$ 2 feet.

Sound waves undergo *absorption, reflection, refraction* and *diffraction* in a manner closely similar to that exhibited by light rays (Chapter LXXVI). For example, sound waves travelling in one medium upon striking another possessing a different density or elasticity are in part absorbed, in part reflected and in part transmitted, the proportions disposed of in each of these ways depending upon the differences between the properties of the two media. Sound waves falling upon a substance such as felt, absorbent cotton or porous fiber board are largely absorbed, whereas those striking water or a hard smooth surface such as glass, steel or a plastered wall are nearly all reflected. A suitably curved concave surface of some hard material is capable of converging the sound waves to form a sound "image." Echoes and reverberations are caused by sounds thrown back towards their source from reflecting surfaces, and whispering galleries in

many instances owe their properties to the architecture of the hall—the walls or ceiling acting as a convex "mirror" to concentrate the sound waves within a small area. Sound is diffracted to a much greater extent than is light, owing to the much greater length (1,000,000 times at least) of the waves of the former. For example, sounds coming through a small open window spread out and fill the whole room just as though the aperture were itself a source of sound.

RESONANCE, FREE AND FORCED VIBRATIONS

Some sounding bodies, such as the strings of a harp, vibrate freely at a certain frequency after the force which set them in motion ceases to act. They are said to be tuned to a certain pitch or frequency; this is called their *natural frequency*. When sound waves corresponding to the natural frequency of such a body fall upon it, it vibrates and gives out the same note as it would if it were actually struck. This phenomenon is known as *resonance* or *sympathetic vibration*. For example, should one raise the dampers of a piano by depressing the loud pedal and sing a note near by or sound one upon a violin or other instrument, the string of the piano vibrates which if actually struck would give the same note—it "sings" in unison with the original tone. Though a resonator gives the maximum response to a sound having the same frequency it also vibrates less strongly to other frequencies a little higher or lower than its own.

A body which possesses no natural frequency is called *aperiodic*. When such is made to vibrate or when one which possesses resonating properties is made to vibrate at a frequency other than its natural frequency, as when a tuning-fork is driven by an alternating electric current, the vibrations are said to be *forced*. In setting up forced vibrations a much greater amount of energy must be expended than in the production of sympathetic vibrations. A vibrating tuning-fork, for example, while it will readily set up vibrations in another fork of its own frequency some little distance away must, in order to cause a body such as a table top to vibrate, be brought into direct contact with it. Vibrations forced in this way stop when the motion which set them up ceases; this phenomenon is due to *damping*.

THE CHARACTERISTICS OF SOUND

Sounds may differ from one another in three particulars, namely, intensity, pitch and quality or timbre.

INTENSITY. Sound intensity and loudness are

not synonymous terms. The former is a purely physical value, whereas the latter refers to the auditory sensation. The sensitivity of the ear varies with pitch, therefore of two sounds having the same intensity but of different pitches, one may be much louder than the other. Intensity refers to the energy (or power) of the sound waves and is proportional to the square of the pressure variations—the amplitude—of the waves; it may be quite independent of the auditory sensation. For example, a tone of a certain high pitch while inaudible, however intense, to the human ear, may be audible to some animals. Sound intensity is therefore given in physical units, namely, the number of dynes (or microwatts) passing through an area of 1 sq. cm.¹ An absolute unit is less generally useful, however, than one which indicates *differences* of intensity. It is now customary to use a scale in which the intensity of a sound is expressed as the logarithm to the base 10 of the ratio of two intensities; this unit is called the *bel* (after Graham Bell, the inventor of the telephone). The number of bels by which one sound intensity exceeds the other is called the *intensity level*. For example, if the intensity of the sound is increased ten times, say from 10^{-10} to 10^{-9} microwatts per sq. cm. the intensity level is raised by 1 bel; a hundred-fold increase in intensity corresponds to a rise in the intensity level by 2 bels, of a thousand-fold by 3 bels and so on. The reference intensity, i.e., the standard with which a given intensity is compared, may be anything we choose, since the bel is a purely relative value. The otologist or physiologist takes as his reference, the intensity of the faintest audible sound in a perfectly quiet room. The sound at reference intensity must be of the same pitch as that of the sound with which it is compared. The following intensity values of a number of common sounds are given by Beatty. The sound of leaves rustling in a gentle breeze has an intensity 10 times that of the faintest audible sound, a whisper at a distance of four feet 100 times, sounds in a quiet street 1000 times, a conversational voice at twelve feet 100,000 times, a loud peal of thunder 10,000,000 times, and sounds at the limit which the ear can endure, 10,000,000,000,000 times. The corresponding intensity levels are 1, 2, 3, 5, 7 and 13 bels, respectively. For

¹ 1 dyne = force which, acting on a mass of 1 gram for 1 second, produces an acceleration of 1 cm. per sec.;
 1 erg = work done by 1 dyne acting through 1 cm.;
 1 watt = 10^7 ergs per sec.; a microwatt = $\frac{1}{1,000,000}$ watt.

physiological or clinical work the bel is inconveniently large. A unit of $\frac{1}{10}$ bel, called the *decibel* (abbrev. db.) is used.²

PITCH is that property of sound which enables one to place a tone at a definite level in the musical scale. It is dependent mainly, though not entirely, upon the vibration frequency, i.e., upon the

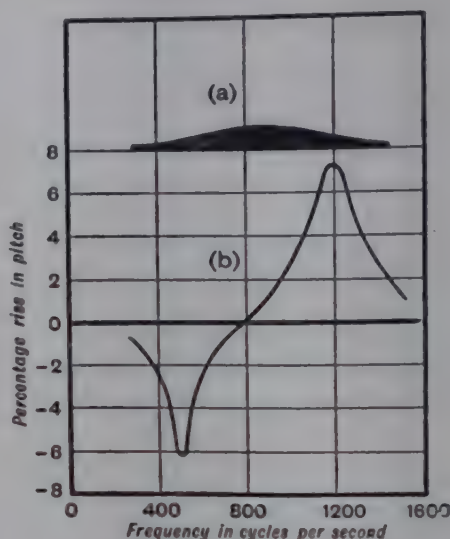


FIG. 480. Illustrating the effect of fatigue upon pitch. (a) The blackened area indicates the distribution of fatigue among nerve-endings due to a 800 ~ tone. Hence the sensation due to a 1200 ~ tone is modified as shown by the curve (b), namely, sharpening of pitch for tones of higher frequency and flattening for lower tones. (From Beatty after Békésy.)

number of cycles falling per second upon the ear. That this property is not entirely a question of vibration frequency is shown by the fact that two sounds of the same frequency but at different in-

² The *sensation level* is defined as the number of decibels that a sound is above the audible threshold of a sound of the same pitch. If the hearing is normal the sensation levels and intensity levels coincide, but are different if the threshold of hearing is raised. The *loudness level*. The intensity level and sensation level and their unit the decibel can only be used for expressing differences between sounds of the same frequency for, as we have seen, loudness varies with pitch. The loudness level is defined as the intensity level of a sound of 1000 c.p.s. At this frequency but at no other do the loudness level and the intensity level coincide. The loudness level of any other pitch is determined by sounding a 1000 cycle tone—the *reference tone*—and raising its intensity until the two sounds are of the same loudness. The number of decibels by which the reference tone exceeds its audible threshold when the two tones are matched gives the loudness level. The energy of a 1000 cycle tone at the threshold of normal hearing is 10^{-16} watts per sq. cm.; this is therefore the zero or reference intensity on the loudness scale. The unit of the loudness level is sometimes called the *phon*. When the sound whose loudness is being measured has a frequency of 1000 c.p.s., decibel and phon are interchangeable terms, but at all other frequencies the latter term is specifically applicable. For example, when a tone has a value of 1 phon, its loudness is 1 decibel above the reference intensity of a 1000 cycle tone, not above that of a tone of its own frequency.

tensity levels may be judged by the ear as differing slightly in pitch.³ When the intensity level of a tone is raised it tends to become "flat" though its frequency remains the same; the pitch may be lowered at very high levels of intensity by as much as half a tone. The alteration in pitch in such an instance is attributed to the greater degree of tension exerted upon the resonating fibers of the basilar membrane (p. 1040), by the louder tone and the rise, in consequence, of their natural frequency of vibration. For example, if fibers which resonate to C are made to vibrate strongly to a loud sound which would ordinarily give that pitch, their frequency rises while the frequency of fibers which ordinarily respond to B is increased to a corresponding extent; they now respond to the loud C. Impulses reaching the cerebral centers are interpreted as having been caused by a tone which under

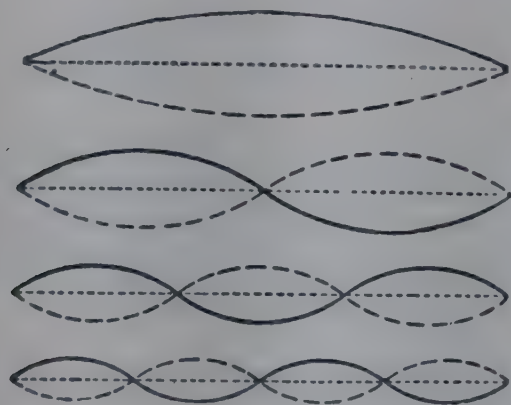


FIG. 481. Shows the form assumed by a string vibrating as a whole and in two, three, and four equal parts, respectively.

usual circumstances would set the B fibers into vibration (see Resonance Theory p. 1040).

The pitch of a note of constant frequency may also change as a result of auditory fatigue (see fig. 480). When the ear is fatigued by a tone, let us say of 800 c.p.s.,⁴ the end organs which are accustomed to respond to this frequency fail to do so or do so inadequately, while those on either side are little affected. As a result, the point of maximal stimulation (p. 1041) undergoes an apparent shift in one or other direction. A tone of a frequency a little lower than 800 c.p.s. therefore is flattened, one a little higher in frequency is sharpened.

THE HARMONIC SERIES AND THE DIATONIC SCALE. A body which executes a simple harmonic or pendular motion (p. 1025), such as the prong of a tuning-fork

³ There is no relation between intensity and frequency. The vibrations of a tuning-fork, for example, become weaker and weaker, i.e., of smaller and smaller amplitude, after it is struck but their frequency remains unaltered.

⁴ c.p.s., as mentioned on (p. 1025), is the abbreviation for cycles per second. It has the same meaning as d.v. (double vibrations).

or a stretched string, vibrating as a whole emits a pure or simple tone and will inscribe a sine curve. Simple tones whose frequencies are such as to form a series in which the higher frequencies are simple multiples of the lowest constitute an *harmonic series*. The ratios of the frequencies are represented by the numbers 1, 2, 3, 4, 5, 6, etc. For example, the frequencies of a series of tuning-forks of which the first vibrates at 250 cycles per second, will be 250, 500, 750, 1000 cycles per second, and so on. Or again, when a string or wire stretched tightly between two fixed points is struck so that it vibrates *as a whole*, it gives out the lowest tone of which it is capable. This is called its *first harmonic* or *fundamental tone*. If a bridge is placed exactly beneath its center, either half of the wire vibrates at just double the previous frequency; if divided into thirds the frequency is trebled. Divisions into quarters, fifths, sixths, etc., give corresponding frequencies. A tone having a frequency double that of the fundamental is called the *second harmonic* or *overtone* or the *octave*.

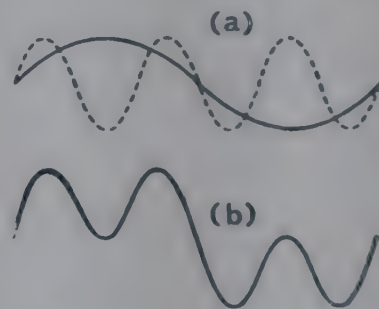


FIG. 482. (a) Wave-form of pure tone of frequency f (solid curve) and of frequency $3f$ (dotted curve). (b) The compound wave.

These considerations lead us to the important *law of lengths*, which states that the number of vibrations per second of a stretched string is inversely proportional to its length. The *laws of diameters*, of *densities* and of *tension* may be summed up in the statement that the vibration frequency is inversely proportional to the diameter of the string and to the square root of its density, and is directly proportional to the weight by which it is stretched. The natural frequency of a stretched string is given by the formula $n = \frac{1}{2l} \sqrt{\frac{T}{m}}$, where n is the number of cycles per second, l the length of string in cm., T the tension in dynes and m the mass of string per cm. of length.

A string when plucked or set into rapid vibration in any way very rarely vibrates with one motion through its entire length; it also vibrates in sections or *loops* which vary in number depending upon the length, tension and mass of the string. The fixed points separating the vibrating sections are called *nodes* (fig. 481). If the string vibrates in halves it gives out not only its fundamental but its octave as well; if it vibrates in thirds the third harmonic is added, and so on. A column of air as in an organ pipe behaves in a somewhat similar manner, giving out a note composed of the

fundamental and a number of overtones. The different motions of the string or air column are imparted to the surrounding air with the production of waves, each of which is composed of the waves caused by the overtones superimposed upon the one due to the fundamental. The composite wave repeats itself at the frequency of the fundamental which therefore determines the pitch of the sound (see Complex Sounds below).

The *diatonic scale* comprises eight notes designated C D E F G A B C', including the fundamental and the octave. C is the fundamental or *unison* and C' the octave. Whatever the actual level at which the scale is pitched⁶ the ratios between the frequency of the fundamental and that of the other tones is constant. The seven notes D E F G A B C' can be produced by dividing a stretched string into 8/9, 4/5, 3/4, 2/3, 3/5 and 1/2 respectively. The frequency of each tone is the reciprocal of the corresponding fraction into which the string is divided, namely, 9/8, 5/4, 4/3, etc., etc. It follows that each tone in the scale also bears a definite ratio to the one below it. The frequency ratios are given below.

Note	C	D	E	F	G	A	B	C'
Ratio to C		9	5	4	3	5	15	
	1	8	4	3	2	3	8	2
Ratio to preceding note	9	10	16	9	10	9	16	
	8	9	15	8	9	8	15	

Two tones having a frequency ratio of $\frac{9}{8}$ or $\frac{10}{9}$ are said to differ in pitch by a whole tone. Those with ratios of $\frac{9}{8}$ are called *major tones* and those of $\frac{10}{9}$ *minor tones*. If the ratio is $\frac{16}{15}$ the difference in pitch is a *half tone* or *semitone*.

The intervals are named according to their positions in relation to the first note of the scale, as follows.

Ratio	Name of interval
1:1	the unison
1:2	the octave
2:3	the fifth
3:4	the fourth
4:5	the major third

In the so-called *tempered* diatonic scale, to which tuning-forks, the pianoforte and certain other musical instruments are tuned, the octave is divided into twelve equal intervals. Each note rises in the scale by a semitone having a frequency exactly 1.05946 times greater than the one below it (1.05946 is the 12th root of 2, the ratio of the octave).

QUALITY OR TIMBRE. That property of sound

⁶ By international agreement the frequency of middle of the piano has been set at 261 c.p.s.

by which one distinguishes between two tones of the same pitch and intensity, e.g., the note of a violin from a bugle note, is called *quality* or *timbre*. It is determined, by the wave form. Sounds can be classified into *noises* and *musical tones*. Noises are defined as sounds (usually disagreeable or at least undesirable) possessing no regular period or definite pitch.⁶ Musical tones are due to waves which are repeated in regular sequence; they may be simple or complex, harmonious or discordant. A simple tone such as that produced by a tuning-fork is usually agreeable but monotonous and uninteresting.

The sound wave of a complex tone is a composite one formed by at least one wave of higher frequency superimposed upon that of the fundamental or simple tone. To the higher frequencies, i.e., to the overtones or harmonics the particular quality of a given musical sound is due. The higher frequencies and the characteristic form of the wave for which they are responsible are produced within the wave length of the lowest or fundamental tone. Thus if the fundamental tone is 100 c.p.s. and waves of higher frequency—200 c.p.s., 300 c.p.s., etc.—are superimposed upon it, then the entire compound wave repeats itself 100 times per second; the pitch of the tone is determined by the latter frequency and its quality by the frequencies and volumes of the overtones (see fig. 482). The ear of the ordinary person cannot readily distinguish the separate overtones, but they are perceived by the trained ear of the musician. A complex sound can be analyzed into its components by means of a series of resonators; when the tone is produced in their vicinity only those resonators respond which have natural frequencies corresponding to the simple tone components. It was shown mathematically by Fourier that any regular periodic vibration can be resolved into two or more simple harmonic motions; the fundamental in all instances having the same frequency as that of the compound wave. This statement is referred to as Fourier's theorem.

The most harmonious sounds are complex tones, especially the combinations of such simple tones as the octaves C and C' (ratio 1 to 2), C and G (ratio 3 to 2) or C, E and G. Any tones whose frequencies are proportional to the simple numbers 1, 2, 3, 4, 5, 6 combine to produce an agreeable sound. Certain other combinations are discordant. According to Helmholtz's theory of harmony, the discordance is due to the production of beats (see p. 1031).

⁶ There are many discordant sounds possessing a regular period of vibration and a definite pitch which though technically classed as musical sounds would certainly be called noises by most persons.

CHAPTER LXXIX

AUDITORY SENSATIONS. THE MECHANISM OF HEARING. THE TELEPHONE AND RESONANCE THEORIES

THE THRESHOLD OF HEARING. The least perceptible sound causes a pressure variation at the ear of $\frac{1}{120000}$ bar¹ or a force of $\frac{1}{120000}$ dyne per square centimeter, or in energy units, about 10^{-9} to 16^{-9} microwatts per square centimeter. These almost incredibly low values are for a sound vibration of 2700 cycles per second but, as already stated, the level of the threshold of hearing is variable, depending upon the frequency of the vibrations. The ear is most sensitive to pitches ranging from 2000 c.p.s. to 5000 c.p.s., i.e., to the upper two octaves of the pianoforte. The maximum sensitivity is for tones of 2700 c.p.s. Below and above the range from 2000 c.p.s. to 5000 c.p.s. the threshold rises rather rapidly (see fig. 483). The lowest audible frequency is about 16 c.p.s., the highest between 20,000 and 30,000 c.p.s. At the upper and lower limits the intensity must be increased enormously above that required for a tone of 2700 c.p.s.; a sound of the lowest frequency in order to be heard must have a pressure of 100 bars and at 20,000 c.p.s. a pressure of 500 bars is required. In terms of energy, that required to make the highest frequency audible is nearly forty million million times greater than is necessary for a note of 2700 c.p.s.

The range of audible frequencies varies considerably between different species. The upper limit is highest in bats; sounds with frequencies far above the audible range of the human ear, namely 98,000 c.p.s. can be heard. It is by means of the high-pitched (supersonic) cries which they emit and the detection of the echo of such sounds from objects in their path during flight that the bat is guided and enabled to avoid collisions.

THE THRESHOLD OF FEELING. When the sound is very loud (at pressure variations above from 10 to 1000 bars, depending upon the frequency) it is

¹ The bar is a unit of pressure and amounts to about one millionth of an atmosphere or to a pressure of 1 dyne per sq. cm. At sea level a decrease in pressure of 1 bar results from a rise in height of 8 mm. At the threshold of audibility for frequencies to which the ear is most sensitive the pressure variation is equivalent to a rise of only about one four hundred millionth part of a millimeter. At such a minute pressure the linear displacement of the membrane has a value comparable with molecular dimensions, or about $1/100,000$ that of the wave-length of green light.

felt as well as heard. The threshold of feeling is highest for frequencies between 250 c.p.s. and 1000 c.p.s., and lowest for those near the limits of audibility. Thus a low rumbling sound is felt more than heard, and a high-pitched shrill note of high intensity arouses a decidedly unpleasant feeling within the ear. For most frequencies pressure variations above 600 bars cause pain and may result in damage to the auditory mechanism. The pain threshold is somewhat lower (between 100 and 200 bars) for frequencies between 2000 c.p.s. and 5000 c.p.s., i.e., for frequencies with the lowest audible thresholds.

The discrimination of differences in intensity and pitch. The least perceptible difference in intensity (ΔI) is dependent upon the original intensity level and also upon the pitch of the sound. For sounds of ordinary intensity and frequency, e.g., tones of musical instruments and of the human voice, a difference of about 25 per cent is just perceptible. This represents a rise or fall of one decibel. It is only within this range of audibility that the Weber-Fechner law (p. 965) is even approximately obeyed. The percentage increase in intensity that is just perceptible is less than 25 at higher and greater than 25 per cent at lower intensity levels. For loud sounds (60 db. or more) the least perceptible intensity difference remains fairly constant at between 5 and 10 per cent over a very wide range of frequencies, whereas a tone near the threshold of audibility and with a frequency of 60 cycles per second must be increased some 700 per cent before any difference is perceived. At low intensity levels $\frac{\Delta I}{I}$ varies with the frequency; it is smallest at 2050 c.p.s. but increases progressively as the pitch is raised or lowered above this frequency.

The sensitivity of the ear for pitch discrimination is greatest over the range from 500 to 4000 c.p.s. The least perceptible difference in frequency (ΔF) varies very greatly in different parts of the scale. Within the range from 500 c.p.s. to 4000 c.p.s. $\frac{\Delta F}{F}$ has a value of 0.003, that is, a change in frequency from 1000 to 1003, from 2000 to 2006 or from 3000 to 3009 and so on, can be detected by the average ear. The trained ear of the musician gives a still lower value. At frequencies near the lower level of audibility $\frac{\Delta F}{F}$ is about 0.01 and near the upper level (16,000 c.p.s. to 20,000

c.p.s.) tones differing very widely in frequency can scarcely be distinguished from one another. Generally speaking, pitch discrimination becomes less acute as the intensity of the sound is reduced.

When the sound intensity is kept at a constant medium value, and pitch discrimination determined over the whole audible scale, there are found to be some 1500 just perceptible differences or steps. When a sound of a constant medium pitch is gradually increased in intensity from the threshold of audibility the number of just perceptible differences in loudness is 325. One might expect that the product of these two figures would give the total number of tones which the ear can distinguish. But, owing to the fact that intensity discrimination varies with the pitch and vice versa, the number of distinguishable tones is only 340,000, not $(1500 \times 325 =) 487,500$.

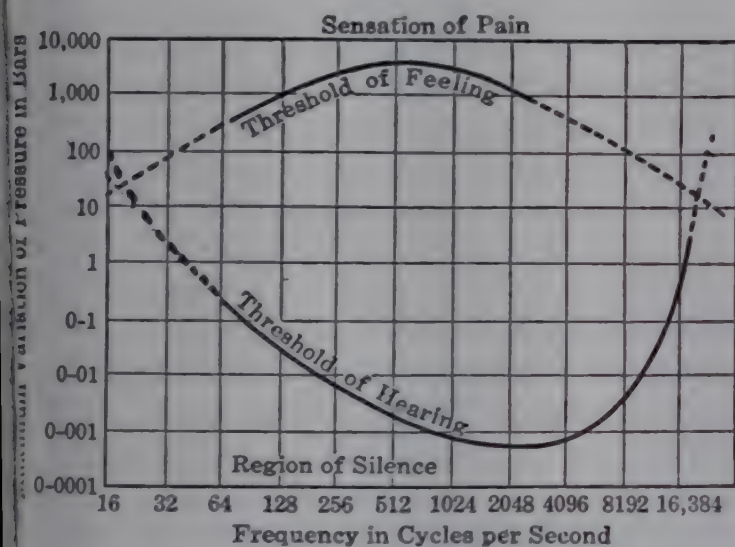


FIG. 483. Chart showing the thresholds of hearing and feeling of sound at different frequencies. (After Vogel, slightly modified.)

MASKING. It is a common experience that a loud sound "drowns" a weaker one. We find it difficult to hear ordinary conversation in the roar of traffic, whereas a whisper seems loud in a quiet church. It is generally true that for any given intensity low-pitched tones have a greater masking effect than those of high pitch, that is, a high-pitched tone is more readily masked by one of low frequency than vice versa. It is not, however, the absolute frequency of the masking tone which is of so much importance, but rather the relative frequencies of the two tones, the greatest masking effect resulting when they are of nearly the same frequency. For example, a greater masking effect is exerted upon a tone of 1000 c.p.s. by a tone of 500 c.p.s. than by one of 800 c.p.s. The phenomenon of masking offers a convenient method of measuring noise. A sound generated electrically by an audiometer (p. 1047) is increased gradually until it is just perceptible to a person of normal hearing in noisy surroundings. Should it be

necessary, for example, to increase the intensity level of the audiometer tone to 50 decibels (i.e., 100,000 times) this value will be the measure of the masking or deafening effect of the noise. Masking is probably responsible for the phenomenon that persons suffering from middle ear deafness frequently hear conversation better in noisy surroundings. In this type of deafness low-pitched tones are usually affected to the greatest extent, and ordinary noise is largely made up of lower frequencies. The normal person, experiencing the effect of the noise upon his own hearing, unconsciously raises his voice which is therefore heard more distinctly by the deaf person (see also p. 1046).

The masking of one sound by another is attributed, upon the basis of the resonance theory (p. 1040), to the overlapping of the vibrations of the two tones upon the basilar membrane. But a tone in one ear is also masked by a louder tone in the other, though to a less degree than when both tones are received by the same ear; this effect must, of course, be of central origin.

The principle of masking is utilized in certain hearing tests. In testing the hearing of one ear a sound which is capable of masking the test tone is applied to the opposite ear by means of an ear-telephone. The possibility of the test tone being heard by this ear rather than by the one under examination is in this way excluded. The masking sound will of course raise the threshold in the affected ear.

THE INTERFERENCE OF SOUND WAVES; BEATS. When two tones of nearly the same frequency are sounded simultaneously they meet in opposite phases (condensations and rarefactions of the air) at one instant and in the same phase at the next. As a result of the alternate interference and reinforcement, the sound undergoes a corresponding waxing and waning. At a certain periodicity it gives rise to a disagreeable throbbing sensation analogous to flicker in vision. Each period of maximum loudness is referred to as a *beat*. According to Helmholtz's theory of dissonance, the jangling or clashing quality of discord which results when certain tones are sounded simultaneously is due to beats produced by interference between the fundamentals or the overtones of the different tones in combination.

The number of beats occurring per second corresponds to the difference between the frequencies of the two tones. For example, if one tone has a frequency of 1000 cycles per second and the other 1100, the rate of beating will be 100 per second. If the frequencies

of the two tones are nearly the same and the beats therefore recur at relatively long intervals—2 or 3 per second—they are heard very distinctly but the sensation is as a rule not unpleasant, and at the slow rate of about 4 per minute they are usually not perceived. Also, like flicker, the beats disappear if they occur very rapidly, i.e., if there is a great disparity between the frequencies of the two tones, a harmonious blend then results or a new tone called a *difference tone* (p. 1034) is heard. At a certain rate of beating between these two extremes the discordance is maximal. The frequency at which the beats disappear, as well as that at which the sensation is most unpleasant, depends upon the pitch of the lower tone, as shown in the following table of the results of Mayer's experiments.

FREQUENCY OF LOWER TONE. CYCLES PER SECOND	NUMBER OF BEATS PER SECOND		INTERVAL BETWEEN TWO TONES AT WHICH BEATS DISAPPEAR
	At which beating most unpleasant	At which beats disappear	
			<i>semitones</i>
96	16	41	6
256	23	58	4
575	43	107	3
1707	84	210	2
2808	106	265	1.5

The sensation of beats in terms of the resonance theory (p. 1040) is explained as being due to overlapping of the vibrations of two neighboring sections of the basilar membrane. Thus the amplitude of vibration of a certain region of the membrane undergoes intermittent variations; corresponding alterations in the intensity of stimulation of the auditory receptors result. The ear, like the eye, is intolerant to this form of stimulation. The greater the difference in frequency of the two tones the greater will be the distance between the two vibrating sections of the basilar membrane and the less tendency will there be for overlapping to occur and for beats to be produced. One would expect then that the spread to resonators on either side of the ones in tune respectively with the two tones would be broader at high than at low intensities and that, as a result of the greater degree of overlapping, beats would be produced at smaller frequency differences in the former instance; such an effect of varying the intensity of the sound can be demonstrated. On the other hand, two tones of nearly the same frequency which when sounded separately are inaudible, may as a result of overlapping give rise to audible beats when sounded simultaneously.

The phenomenon of beats has an interesting application in the detection of fire damp in coal mines. This gas, being lighter than air, transmits sound at greater velocity; a column of this gas has therefore a higher vibration frequency than a column of air of the same dimensions. (The vibration frequency of a column of

gas is proportional to the time taken for the sound wave to pass through it.) Two long tubes or whistles similar in every way are filled, one with the suspected mine air, the other with pure air. The two whistles are blown simultaneously; if much fire damp is contained in the air of the first tube, the frequency of the sound vibrations will not be the same in it as in the one filled with pure air, and beats will be heard. The concentration of the dangerous gas is estimated from the rate of beating.

THE LOCALIZATION OF THE DIRECTION OF THE SOURCE OF A SOUND. A visual sensation is projected very accurately to a definite point in the outside world, i.e., an object in the visual field forms an image upon a corresponding part of the retina. Sound "images" cannot, of course, be localized in the same way upon the auditory receptors, there being no spatial correspondence between the sounding body and the basilar membrane. In the judgment of the direction of a single brief sound or of an intermittent sound the most important factor is the difference in the arrival times of the sound at the two ears. If the sound reaches both ears simultaneously, it is projected to the mid-line in front or behind the head, but if the vibrations are not received at the same instant by the two ears the sound is located on the side of that ear which is stimulated first. An illusion of a sound changing its direction may be created by means of two watches which tick at slightly different rates held one to each ear. Just as with any two movements of different frequencies, the time intervals between the ticks of the two watches lengthen and shorten periodically (fig. 484). When the two ticks fall simultaneously upon both ears, a single sound is heard in the median plane either in front or behind. An instant later when the ticks become asynchronous the sound moves to the side of the faster tick, but as the intervals between the sounds lengthen they are heard separately by each ear; then as the intervals shorten again a single sound is heard which now seems to come from the side of the watch with the slower tick. Thus the sound image seems to move continuously around the head.

The effect upon sound localization of varying the time interval between the stimulation of the two ears can also be demonstrated in the following manner. A stethoscope in which the length of tubing of one limb can be altered (fig. 485) receives sound vibrations from in front and in the mid-line. When the pathway is lengthened by extending the tubing of the adjustable limb the

sound reaches the opposite ear first, and therefore seems to come from that side; upon shortening the tubing the sound is located on the side of the shorter limb.

The maximum difference in the arrival times of a sound in opposite ears at which the separate sensations fuse into one is determined by the length of the path from ear to ear, namely, 21 cm. (directly through the head). Sound is transmitted this distance through air in 0.00063 second and through the longer distance around the obstruction caused by the head in a somewhat longer time. The greatest interval between the arrival of a single sound at each ear is therefore a little longer than 0.00063 second, and this is the maximum interval between two sounds which when led to separate ears should be heard as one. By actual measurement it has been found that at intervals greater than about 0.00180 the two sounds are heard separately. The ear through experience discounts a time interval caused by the difference in distance of the two ears from the origin of the sound but recognizes any greater time interval as being due to separate sounds.

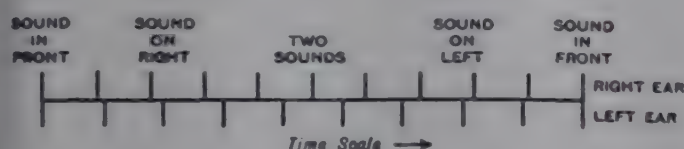


FIG. 484

The localization by the ear of a *continuous sound* cannot be explained by an interval between the reception of the sound by the two ears. When the vibration frequency is less than 800 c.p.s. a difference in phase of the sound waves striking opposite ears is the most important factor. Waves emitted from a source in the mid-line reach the two ears simultaneously and the sound is localized accordingly, but if the sound comes from one side the crest of the wave will reach the ear of that side an instant before it reaches the opposite ear. When the length of the sound wave is double the distance between the ears, namely, 42 cm., the waves fall upon the two ears in opposite phases; the wave cannot then be said to be in advance or behind the other. The ear cannot distinguish between the two phases; the sound is localized with difficulty, seeming to come from all sides. The uncertainty in localization becomes evident around 800 c.p.s. (length of wave about 42 cm.). At frequencies above from 800 c.p.s. to 1000 c.p.s. localization by phase difference fails. High-pitched sounds such as the chirp of a cricket are very difficult to locate and often seem to come from several directions at once. Some information

as to the direction of high tones is gained, however, from *differences in the intensity* or in the *quality* of the sound in the two ears. Simple tones of low pitch cannot be located through a difference in intensity in opposite ears owing to the great length of the waves (measured in feet or meters) as compared with the dimensions of the head. That is to say, the head casts no shadow for low-pitched sounds. On the contrary, sounds of high frequency (short wave length) coming from one side are shielded from the opposite ear by the head, and the difference in intensity of the vibrations in the two ears is used as a clue to the direction of the sound. The shielding effect of the skull also plays a rôle in the localization of a complex sound situated on one side or behind, even though it is of low pitch, because the higher frequencies (overtones) are screened by the skull

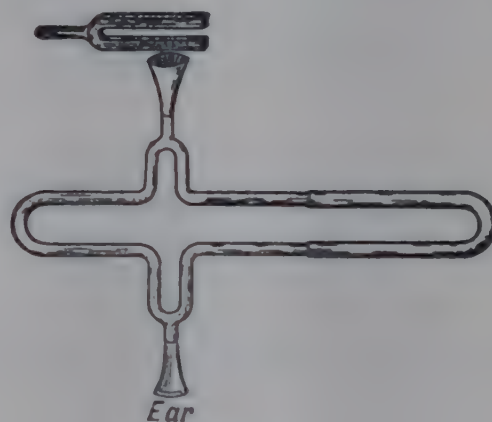


FIG. 485

and the auricle; the alteration in the quality of the sound caused thereby then serves as a clue. This factor is important particularly in deciding the direction of familiar sounds, i.e., those, such as voices, which have been heard upon previous occasions from different angles and hence have had their qualities impressed upon the memory.

In the localization of sounds with frequencies below 800 c.p.s. it would obviously be an advantage to have the two receptor organs separated by a greater distance than 21 cm., for any phase difference would be increased thereby. In World War I this was recognized; an apparatus consisting of two microphones separated by a difference of about two feet and connected by tubing to the ears of an observer was employed for locating enemy aircraft in flight. The application of the principle is also seen in the insect world; certain forms have paired sets of auditory receptors separated as widely as possible from one another, namely, on either side of the thorax or abdomen or, as in crickets and grasshoppers, just below the knee joints.

THE MECHANISM OF HEARING

THE EXTERNAL EAR

Though the shape of the auricle suggests that it might serve as a concave reflector to concentrate sound vibrations and direct them into the auditory meatus, its small area as compared with the length of the waves of ordinary sound, negatives the idea that it acts in this manner to any important degree. Only sounds of relatively high frequency (over 6000 c.p.s.) whose wave lengths are commensurate with the size of the auricle could be converged in this way; longer waves would tend to be scattered. The large trumpet-shaped ears of some animals, on the other hand, are of such a size as to be of real service in this respect, especially since they can be turned towards the source of the sound.

THE TYMPANIC MEMBRANE is aperiodic. That is, it vibrates unselectively to a wide range of frequencies, having no natural frequency of vibra-



FIG. 486. The response of the ear-drum to a simple sound. The unsymmetrical nature of the human ear results in parts of the simple harmonic curve, which is drawn thick, being replaced by those shown by broken lines. (After Jeans.)

tion; or rather, its natural frequency lies below the threshold of hearing. Like the well-designed diaphragm of a telephone transmitter, it does not resonate to any particular frequency but responds to all. It is forced into vibration by the sound waves and exhibits a high degree of damping, its movements stopping almost instantly upon cessation of the sound.

The tympanic membrane does not faithfully reproduce the *form* of the incident sound waves, but modifies them, the new vibratory motion being then transmitted through the ossicles to the internal ear. This behavior of the membrane is due to its asymmetry. A structure, such as the prong of a tuning-fork or the skin of an ordinary drum which is perfectly elastic and symmetrically loaded moves equal distances on either side of its resting position, its movements in response to a pure tone being simple harmonic and can be represented by a sine curve. The asymmetry of the ear drum is due mainly to the auditory ossicles to which it is connected on its inner aspect, and to the tension exerted by the intra-aural muscles.

TONES CREATED BY THE EAR; AURAL HARMONICS; COMBINATION TONES. The asymmetry of the drum membrane results in the production of tones by the ear itself, i.e., additional tones with frequencies differing from those of the incident sound. The curve in fig. 486 represents the movements of the drum membrane to a *pure* tone of 100 c.p.s. Upon analysis this curve is found to be compounded of a series of simple harmonic waves having frequencies of 200 c.p.s., 400 c.p.s., 600 c.p.s., etc. The compound wave repeats itself 100 times per second, so the original tone as well as the higher frequencies is heard. Thus, as a result of the asymmetry of the drum membrane the ear has created a new set of frequencies, adding to the original tone the octave (200 c.p.s.) and the other harmonics. These overtones, called *aural harmonics*, being purely subjective, i.e., non-existent outside the ear, cannot, of course, be detected by means of resonators.

The aural harmonics are not heard, especially those of higher frequency, unless the original sounds are fairly loud (over 45 decibels) for it is only when the vibrations reach a certain amplitude, and force the drum membrane and the structures of the middle ear to their elastic limits that they become asymmetrical. As the intensity of the sound is progressively increased harmonics of higher and higher frequencies are added to the original tone. The latter, however, always tends to obscure (mask) to a certain degree the higher frequencies. With vibrations of small amplitude, movement at the incudomalleolar joint permits equal displacements of the membrane in both directions. Also, when this joint is ankylosed, as in old age, outward and inward movements tend to become more nearly equal and the subjective tones are absent or greatly reduced. The tensor tympani muscle, by drawing the malleus inwards, tends to reduce the movement at the incudomalleolar joint. Increased tension of this muscle therefore tends to increase the aural harmonics, relaxation to diminish them.

Combination tones. When two pure tones are sounded, the ear adds not only the octave of each tone, but a *difference tone*, so called because its frequency is the exact difference between the frequencies of the two primary tones. For example, when tones with frequencies of 200 and 300 cycles per second are sounded together a compound motion will be produced which repeats itself 100 times per second. Tones of 100, 200, 300, 400, 500, 600 c.p.s., etc., will be heard. The frequencies 200 c.p.s. and 300 c.p.s. are, of course, those of the two primary tones and 400 c.p.s. and 600

c.p.s. are their octaves; 100 c.p.s. is the "difference" tone and 500 c.p.s. (the sum of the original frequencies) is called the "summation" tone.² The summation tone is always more difficult to hear than the difference tone since, being of higher frequency and weaker, it tends to be masked by the primary and difference tones.

The difference tone of 100 c.p.s. in the foregoing example is the fundamental of the tones 200 c.p.s. and 300 c.p.s., and it is generally true that whenever two or more tones which happen to be the harmonics of the same fundamental tone are sounded together with sufficient intensity, the fundamental is heard as a difference tone, i.e., the fundamental tone is created by the ear. To give another example, when the second (octave) and the third harmonics of middle C are sounded simultaneously (respective frequencies are 512 c.p.s. and 768 c.p.s.) middle C itself (256 c.p.s.) is heard.

These facts have important practical applications in telephone, talking picture and radio engineering. The diaphragm of a telephone is so constructed that it responds to the harmonics of the human voice but not to the main tones; these are added by the ear of the listener. The natural frequencies of the instrument range from 300 to 2400 c.p.s., which are above the frequencies of the main vocal tones. The latter are therefore transmitted at a scarcely audible intensity, whereas the higher frequencies—the harmonics—since they coincide with the natural frequencies of the instrument are strengthened. The deeper main tones are created by the ear. By this device exaggeration of certain of the more prominent tones of the voice is avoided. Otherwise these tones through resonance would mask other tones of higher frequencies and lower intensity which are largely responsible for the quality and intelligibility of speech. The principle has been demonstrated in a striking manner in the laboratories of the Bell Telephone Company. Two sets of gramophone records were made. A song, a conversation, instrumental music and other sounds were reproduced on one set, all the tones being faithfully recorded. The other set of records were made from the same sounds after they had been passed through filters and the fundamental tones removed. To the ear both sets of records were almost identical.

THE TRANSMISSION OF SOUND FROM THE DRUM MEMBRANE TO THE INTERNAL EAR

The vibrations of the tympanic membrane set up by air-borne sounds are transmitted to the oval window by the chain of auditory ossicles and thence to the perilymph of the vestibule. Vibra-

² Difference and summation tones are not always subjective, for under certain conditions they are produced outside the ear, as when the sounds are transmitted through some medium which like the tympanic membrane is asymmetrical, e.g., the rectifying valve of a radio set.

tions of audible frequencies are transmitted through Reissner's membrane and the scala media to the basilar membrane, then through the scala tympani to the round window (fig. 487). The compression phases of the sound waves in the external auditory meatus cause a movement inwards of the tympanic membrane and of the base of the stapes, a downward displacement of the basilar membrane and a movement outwards (i.e., towards the tympanum) of the round window. During the expansion phases of the sound waves, displacements of these structures in the reverse direction occurs. Thus are the vibrations of the drum membrane reproduced in the basilar membrane.

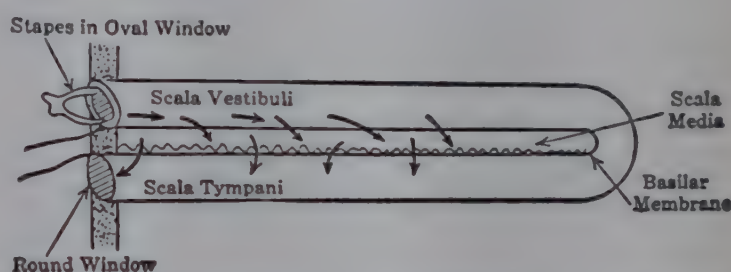


FIG. 487. Diagram of the passages of the cochlea straightened out to show the manner in which vibrations are transmitted from the oval to the round window through the scala media. The wavy line represents the organ of Corti.

It is quite evident that, since liquids are incompressible, no appreciable movement of the stapes could occur were there no part of the bony labyrinth which yielded to pressure. The membrane of the round window situated between the scala tympani and the middle ear yields readily, and thus permits such a movement to take place. Owing to the presence of the helicotrema (p. 1022) through which the scala vestibuli communicates with the scala tympani, vibrations of very low frequency are incapable of setting up vibrations in the membranous cochlea of sufficient force to stimulate the nerve endings; the fluid is moved *en masse* as in a U-shaped tube formed by the upper and lower galleries.

The middle ear is filled with air; vibrations of the drum membrane must therefore be transmitted to the round window as well as to the oval window. The auditory ossicles, however, provide a preferential path for the transmission of sound, serving as a mechanism for concentrating the vibrations at the internal ear. Any inward movements of the membrane of the round window which may result, since they will be opposite in phase to those of the base of the stapes, will tend to diminish rather than to enhance the force of the vibrations

of the basilar membrane. It has been found, for example, that shielding the round window by means of a pledget of cotton placed over the niche in which it lies increases the acuity of hearing.

Two factors are responsible for the intensification of the vibrations at the oval window, (a) the leverage action of the malleus and incus and, (b) the greater area of the drum membrane as compared with that of the oval window. The malleus and incus together form a bent lever of the first class, the handle of the malleus constituting the long arm of the lever and the long process of the incus, which articulates with the stapes, the short arm (see fig. 488). The axis of rotation (fulcrum) of the lever is represented by a line running through the anterior ligament of the malleus and the short process of the incus. The length of the short arm is about $\frac{2}{3}$ that of the long arm formed by the handle of the malleus. The amplitude of movement of the tip of the incudal arm is therefore only $\frac{2}{3}$ that of the tip of the long arm, i.e., the amplitude of movement at the center of the drum membrane. The matter is complicated by the fact that the base of the stapes is not moved in and out in a simple push-pull or plunger-like action but, being hinged at its posterior margin,³ executes a rocking motion; the amplitude of the movement of the posterior part of the footplate is considerably less, therefore, and that of its anterior edge considerably greater than $\frac{2}{3}$ that of the drum membrane. Should the sound be excessively loud (i.e., near the threshold for pain) the footplate, instead of moving as just described, pivots around a longitudinal axis passing through its center (Békésy). The delicate structures of the internal ear are further protected from violent vibrations by the momentary dislocation of the incudomalleolar articulation. Instead of engaging in the usual way the surfaces glide over one another, like a slipping motor clutch, with consequent loss of energy and reduction in the amplitude and force of the vibrations. The protective rôle played by the intra-aural muscles has been mentioned (p. 1021).

The ratio of the long arm of the lever to the short arm being 3 to 2, one would expect an increase of $\frac{3}{2}$ in the force delivered at the oval window over that incident upon the tympanic membrane. Actually, the energy lost in transmission (in overcoming the inertia of the ossicles)

³ According to Wilkinson, the base of the stapes pivots around an axis passing through the junction of its posterior and middle thirds.

and the damping effect of the surrounding air more than offset the mechanical advantage gained by leverage. Were no other factor involved the vibrations would have a force only half as great at the oval window as at the drum membrane. But the area of the latter is some 20 times greater than that of the oval window. This alone by concentrating the sound waves would increase their force upon the smaller area twenty-fold. But the loss in transmission, as just stated, is about 50 per cent; which means that the force incident upon the drum membrane is about $\frac{1}{10}$ of that upon the oval window. This increase in force of the vibrations with relatively little change in amplitude is of considerable importance. It appears that a change of just such a nature is required for the most efficient transference of vibrations from a medium of low resistance, namely air, to

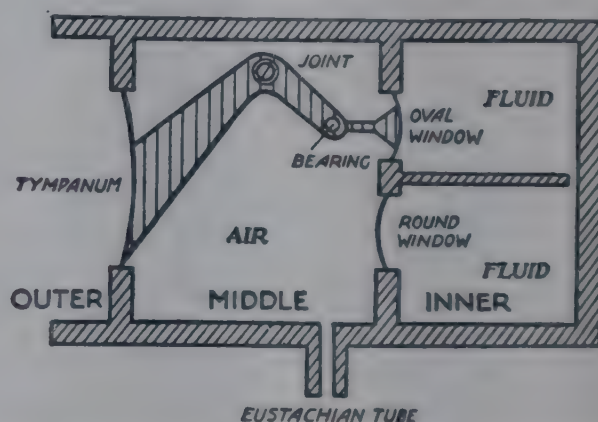


FIG. 488. Model illustrating the transmission of sound vibrations from the drum membrane to the organ of Corti. (From Lythgoe after Beatty.)

one of greater density and high resistance, such as the fluid of the internal ear.

BONE CONDUCTION. The auditory receptors are stimulated by sound transmitted through the bones of the skull. In man the most direct and effective bony pathways for the conduction of sound to the internal ear is furnished by the trabeculae in the subaditus region. Injury to this region, as by fracture, results in impairment of bone conduction. In order for sound to be perceived to any important extent through bone the sounding body must be in contact with the skull (e.g., mastoid process); bone conduction of air-borne sounds impinging upon the head is very slight. The sound is transmitted through the bone as through any solid, as a train of alternating compressions and expansions. Owing to the presence of the oval and round windows, chiefly the latter, serving as outlets for pressure variations, adequate movements of the basilar membrane are permitted to take place. When the base of the footplate is immovably fixed in the oval window, the round window alone serves such a purpose. The waves of compression, according to

Békésy, exert their effect mainly upon the semicircular canals from which fluid is forced into the vestibule. For this reason, and also owing to the greater resistance offered at the oval window, the pressure in the scala vestibuli is elevated more than that in the scala tympani. With each wave of compression the basilar membrane therefore moves downwards and the membrane of the round window outwards.

In a person with normal hearing, obstructing the external auditory canal by the finger increases the loudness of bone-conducted sound. This is attributed to the compression of the air in the canal by the vibrations of the skull, the sound being thus transmitted through the ossicles to the internal ear as in ordinary air transmission. The threshold for bone conduction is given by Békésy as 3.5×10^{-9} cm. movement of the skull for a tone of 800 c.p.s.

STIMULATION OF THE HAIR CELLS. The tips of the hair cells are embedded in the under surface of the tectorial membrane. An upward movement of the basilar membrane should cause bending of these processes and compression of the bodies of the cells; a downward movement of the membrane would, on the other hand, cause traction upon the processes, and possibly some elongation of the bodies of the cells. It is not definitely known which of these movements is responsible for the stimulation of the nerve endings. The nature of the immediate stimulus is also a matter for conjecture; it may be mechanical, electrical (see cochlear potentials, p. 1038) or chemical. A theory of chemical stimulation has been proposed by Hallowell Davis. He suggests that the compression of the sensory cells by the upward swing of the basilar membrane, i.e., when the base of the stapes moves outwards, causes the liberation of a chemical substance which, acting upon the sensory endings, sets up the nervous discharge.

THEORIES OF PITCH PERCEPTION

There has been relatively little room for dispute concerning the functions of the middle ear. The mechanism of the internal ear, on the contrary, has been for many years a subject of lively controversy to which both physiologists and physicists have contributed. The appreciation of pitch has been the pivot around which discussions of cochlear functions have turned, and the several theories which have been proposed are attempts to explain this extraordinary faculty of the auditory mechanism.

All theories of hearing can be divided into two main categories. In one group (a) are placed those theories which attribute the estimation of

pitch, and in consequence the ability to analyze a complex sound into its components, to the cerebral centers, and in the other (b) those which maintain that sound analysis is purely a function of the cochlea. None of those coming under the first heading is acceptable as a complete theory of hearing; one, namely the telephone theory, will be briefly described.

The telephone or frequency theory was formulated by Rutherford in 1886. The diaphragm of a telephone transmitter converts sound vibrations into electrical impulses (actually, rhythmical variations in current strength) of the same frequency. The electrical impulses conveyed by wire to the receiver of the instrument set up vibrations in a diaphragm which reproduces the original sound. If we substitute the basilar membrane for the diaphragm of the telephone, the electrical impulses for nerve impulses, the wire for the auditory nerve and the reproduced sound in the receiver for the auditory sensation, we then have a rough outline of the telephone theory of hearing. In this theory the basilar membrane is supposed to vibrate as a whole, i.e., like the diaphragm of the telephone transmitter, not selectively according to the principle of resonance. The telephone theory postulates, therefore, that *the cochlea possesses no faculty of sound analysis, the frequency of the impulses transmitted over each fiber of the auditory nerve being the sole basis for the estimation of pitch.* The intensity of sound is, according to this theory, a function of the number of active nerve fibers.

The relatively low frequency (less than 1000 per second as compared with from 20,000 to 30,000 c.p.s. for the highest audible pitch) at which the nerve fiber can conduct impulses has always been an insuperable objection to the telephone theory. This point will be discussed in the next section.

THE WEVER AND BRAY PHENOMENON

In 1930 Wever and Bray made the surprising discovery that spoken words and other sounds entering the ear of a decerebrate animal were faithfully reproduced when electrodes were placed upon the auditory nerve and connected through a valve amplifier with a telephone receiver or loud speaker. It was at first thought that the sounds emitted by the telephone receiver were due solely to action currents (i.e., to nerve impulses) of the same frequency as the sound vibrations received by the animal's ear. If this were true it would mean, of course, that the quality of sensation is correlated with the frequency of impulses in the nervous discharge and would therefore be con-

trary to observations upon other senses, for all recent work indicates that impulse frequency varies only with the *intensity* of the stimulus. Such a conclusion implies also that the analysis of sound is a function of the cerebral cortex, as postulated by the telephone theory. As a result fresh interest in this theory was aroused.

Saul and Davis in later experiments demonstrated that there are two components in the electrical potentials picked up from the nerve, namely, *true action potentials* (nerve impulses) resulting from the excitation of auditory nerve endings in the cochlea, and electrical potentials generated within the cochlea as a result of the distortion of non-nervous structures by the sound waves. These latter effects are referred to as the *cochlear response*, *aural microphonics* or *cochlear potentials*. In records showing both types of electrical effect the action potential waves are superimposed upon the aural microphonics.

The cochlear response differs from the action potentials in the following respects. General anesthesia abolishes the action potentials but not the microphonic effect. The action potentials are also affected much more by cooling the cochlea, and they disappear much sooner after the death of the animal. Arrest of the blood supply to the cochlea rapidly abolishes both responses. The latent period of the action potential (up to 0.83σ) is much longer than that of the aural microphonics (0.1σ). The cochlear potentials can be recorded from any part of the internal ear or even from any part of the skull, provided that the amplification is adequate. (They are obtained most readily with the differentiated electrode at the round window and the indifferent electrode inserted into the muscles of the neck.) The action potentials can be recorded only from the auditory nerve or some part of the auditory pathway, e.g., cochlear nuclei of the medulla, lateral lemniscus, etc. The cochlear potentials have a much greater tendency to spread through the tissues, especially over meningeal surfaces; it is owing to such spread that they can be picked up from the auditory nerve. The waves of the two responses differ in shape, the wave form of the cochlear potential being almost identical with that of the stimulating sound. The action potentials synchronize with the sound waves up to a maximum of 3000 per second (see p. 1039), whereas the cochlear potentials follow the vibration frequency up to 16,000 cycles per second, and it is probable that with more delicate methods of recording a correspondence between the cochlear potentials and the sound waves up to the limit of audible frequencies, namely, 20,000 or more cycles per second, could be demonstrated. Finally, the cochlear potentials

show summation, whereas the action potentials are of course "all or none."

Several theories as to the mode of origin of the cochlear potentials have been offered. Davis and his associates believe that they are due to pressure variations upon the hair cells induced by the sound waves; they therefore come under the head of *piezo-electric currents* such as are generated by pressure upon a quartz crystal. According to Davis, a potential difference is created between the bases and free ends of the hair cells when these cells are compressed against the overlying tectorial membrane, that is, when the footplate of the stapes moves *outwards* and the basilar membrane swings upwards. In support of his contention Davis cites experiments upon animals (albino cats and waltzing guinea-pigs) in which the organ of Corti was congenitally absent or the hair cells *abnormal* and no aural microphonics could be obtained. Moreover, certain chemicals, e.g., crystals of sodium chloride, applied to the internal ear injure the hair cells and depress the cochlear response, and when degenerative changes were induced in the mid-region of the basilar membrane of dogs by a loud tone of *medium pitch* (p. 1042) sounded over a long period, this particular sound was not heard by the animal nor was it followed by a cochlear response.

The physiological function, if any, of the cochlear potentials is unknown. They appear to be rather of an accidental occurrence—an epiphenomenon of auditory function. However, this much can be said; hearing may be lost though the aural microphonics persist unimpaired, but hearing is never retained in their absence.

Evidence that vibrations of resonant structures in the cochlea are responsible for the aural microphonics has been secured by Walzl and Bordley. They have succeeded in injuring selected and limited regions of the organ of Corti, without separation of Reissner's membrane on the basilar membrane; and have studied the effects of such injuries upon the cochlear potentials. Damage near the base of the cochlea was found to raise the threshold for high tones, while injury near the apex was followed by impairment or loss of the response to sounds of low frequency. These results point to elements—most probably the hair cells of the organ of Corti—attached to a particular level of the basilar membrane, and thus tuned to particular sound frequencies: they give strong support for a place theory of hearing (p. 1041).

Impulses recorded from the auditory nerve and brain. Action potentials free from microphonic effects can be picked up from the auditory nerve

by means of coaxial electrodes (described on p. 786). The latency of the action potentials is between 0.53 msec. for sounds of the highest intensity and 0.83 msec. near the threshold of audibility. The impulses are synchronous with the sound waves up to about 3000 c.p.s.; above this frequency there is no correspondence between the two. When a sound with a frequency less than 900 c.p.s. is gradually increased in intensity a point is reached at which the action potential is maximal. If the intensity is kept at this level but the frequency raised above about 900 c.p.s., the amplitude of the waves falls sharply to about half of their previous value; at 2000 c.p.s. the amplitude is reduced to one-third and at 3000 c.p.s. or so, to a very low value. It must be remembered that the electrodes placed upon the intact nerve record potential changes from a number of fibers almost simultaneously. The recorded waves are, therefore, composite in nature and vary in amplitude with the number of functioning fibers. The step-like fall in amplitude as the frequency is raised from 900 to 3000 c.p.s. is due to a corresponding reduction in the number of active fibers and this reduction is the result, in turn, of the impulses falling each in the relative refractory period (p. 787) of its predecessor. Now the absolute refractory period of a fiber of the auditory nerve is about $\frac{1}{1000}$ second. In other words, a single fiber cannot conduct more than 1000 impulses per second. Therefore, when the sound vibrations reach a frequency of between 900 and 1000 c.p.s., the fibers respond only to every other stimulus. But the refractory periods of all the fibers do not begin and end at the same instant; this allows half the fibers to respond to *alternate* vibrations and the nerve as a whole to respond to every vibration though, as just stated, the amplitude of the action potential is reduced by half. At a vibration frequency of 2000 or 3000 c.p.s. the individual fibers respond to every third or fourth vibration, respectively. Yet again, since the refractory periods are not coterminous, the fibers function in *rotation*, and the nerve as a whole is capable of answering to every stimulus; the amplitude of the action potential is diminished in proportion to the number of inactive fibers.

Thus, the limited correspondence of the auditory impulses with the frequency of the stimulating sound is a phenomenon which is due, apparently, to the fact that the auditory nerve is a composite record of the potentials in a number of separate nerve fibers. The fiber responds to a definite

phase of the stimulating wave-cycle, but each fiber in a group does not necessarily respond to the same wave; so, the frequency of the impulses in a *single fiber* may be very much lower than that of the stimulating sound. Galambos and Davis have recorded the impulses from a single fiber by means of a glass microelectrode inserted into the auditory nerve. The nerve was exposed through an opening in the temporal bone and the electrode adjusted by a micromanipulator until a single series of impulses appeared in the record. The findings of Galambos and Davis are entirely in accord with a place theory of hearing (p. 1041). The isolated auditory fiber was found to behave in the same manner as does any other sensory nerve. At threshold intensity it responded to a narrow band of sound frequencies; the impulse frequency varied only with changes in the *intensity* of the sound. The maximum frequency of the impulses, 400 per second, was recorded when the sound was increased to 30 decibels above threshold intensity. At the higher sound intensities the fiber reacted less specifically, responding to frequencies within a wider range. In some instances a very loud sound, even an octave below the band of frequencies to which the response of the fiber was restricted at threshold intensity, caused a discharge of impulses.

Impulses can be recorded by means of electrodes inserted at various levels along the auditory pathway, e.g., the cochlear nuclei, the trapezoid body, the lateral lemniscus, the medial geniculate body or the inferior colliculus, and even from the auditory radiation and auditory cortex. At the higher levels the frequency at which synchronization of impulses and sound waves ceases is much lower than in the auditory nerve. The number of synapses which the impulses must cross is apparently the factor responsible for depressing the synchronization limit. At the inferior colliculus synchronization is not evident, as a rule, above frequencies of 1000 c.p.s. and not above 20 c.p.s. in the auditory radiation or cerebral cortex.

Now the highest audible frequency is from 20,000 to 30,000 cycles per second (p. 1030). It is quite evident therefore that the telephone hypothesis or any other based upon the assumption that the brain receives impulses of the same frequency as that of the incident sound can no longer be entertained.

The organ of Corti is projected to the medial geniculate body, which constitutes the primary auditory center, and to the acoustic area of the

cerebral cortex. In both these regions a spatial differentiation according to sound frequencies has been demonstrated. The dorsal part of the medial geniculate body responds to frequencies of around 8000 c.p.s., the anterior and lateral parts to 4000 and 2000 c.p.s., respectively, and the posterior part to 1000 c.p.s. Cycles of 500 per second and less are recorded in the central portion. In the acoustic area the apical turns of the organ of Corti are represented anteriorly and the basal turns posteriorly.

THE RESONANCE OR HARP THEORY

Though it was suggested as long ago as 1761 by Cotugno of Naples and in 1826 by Sir Charles Bell of Edinburgh that the ear owed its faculty of pitch perception to resonating structures in the labyrinth, it was not until 1863 that the scientific foundations of the resonance theory were laid. In this year Helmholtz published his now famous work entitled *Sensations of tone as a physiological basis for the theory of music*, in which he gives an account of a brilliant series of physical and physiological studies of hearing.

The resonance theory postulates that the analysis of sound into its constituent frequencies is primarily a function of the cochlea, that the fibers of the basilar membrane constitute a series of resonators, and that the part or level of the membrane at which the fibers are set into maximal vibration by the sound waves is the sole basis upon which the brain rests its judgment in discriminating differences of pitch.

The fibers of the basilar membrane which in deference to the resonance theory are frequently referred to as the *auditory strings*, number about 24,000. Each arch of Corti, of which there are some 5000, is associated with 4 or 5 auditory strings. The combined structure, rather than each one of the 24,000 fibers, should probably be regarded as a resonating unit. In this theory the resonating structures are compared to the strings of a harp or pianoforte; they are believed to vibrate in sympathy with the sound waves, i.e., each resonator responds to the frequency corresponding to that of its own free vibration (p. 1026). We have seen (p. 1023) that the fibers increase progressively in length from the base to the apex of the cochlea, a fact quite in accord with the resonance theory.

Upon first thoughts one would likely conclude that this resemblance of the basilar membrane to a stringed instrument must be mere coincidence

and that it is rather fantastic to compare a structure only 30 mm. long and 0.5 mm. wide at its broadest part with a piano or harp in which the longest (bass) wires are measured in feet. Furthermore, the auditory range is some 11 octaves and some 1500 separate tones can be distinguished by the ear, whereas the pianoforte extends over only 8 octaves, containing some 96 separate notes. But factors other than length, namely, tension and mass (p. 1028) determine the vibration frequency of a stretched string. There is reason to believe that the basilar fibers are differentiated as to tension, the loosely stretched fibers being at the apex where the flimsy character of the external spiral ligament seems to indicate that it exerts here the minimum degree of traction upon the basilar membrane. In the basal turn the external spiral ligament is several times thicker than at the apex,

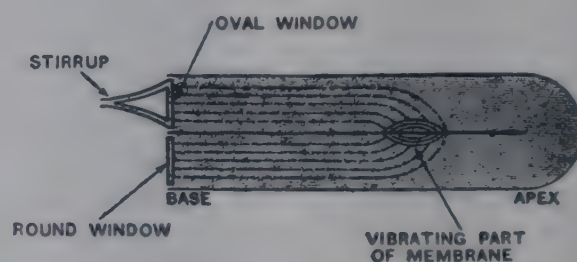


FIG. 489. Illustrating liquid loading of the auditory strings. See text. (After Beatty.)

which suggests that in this part of the cochlea the basilar fibers are at their greatest tension. Yet, even granting that the longest auditory strings are at minimum tension, their mass would need to be greatly increased in order that they should be capable of vibrating at the lowest audible frequency, namely, 16 cycles per second. Now, the bass strings of the piano are, of course, of greater length and lower tension than the strings of the treble, but their low frequency of vibration is secured largely by increasing their mass. The greater mass is obtained not so much by increasing the thickness of the wire (for this would greatly reduce its flexibility) but by a helix of copper wire, i.e., by a wire coiled around it. By means of such loading of a comparatively short thin wire, a vibrating element is obtained with a low frequency yet sufficiently flexible and of convenient length.

The auditory strings are loaded by the cellular structures of the basilar membrane (see p. 1023) and also, to a greater extent, by the fluid in which they are immersed. This liquid load, according to Wilkinson, is the column of fluid extending upwards from the oval and round windows to the

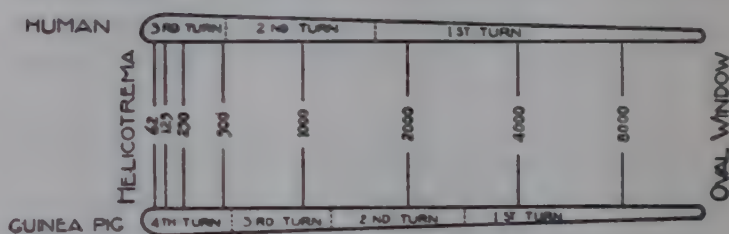
basilar fibers resonating at the moment. The length of the fluid column will vary, of course, with the level of the vibrating fibers, i.e., with their distance from the oval and round windows.⁴ According to this conception of liquid loading the auditory strings are differentiated with respect to mass as well as according to length and tension, the shortest fibers at the base of the cochlea (i.e., nearer the oval and round windows) being loaded with the shortest liquid columns, the fibers at the apex with the longest columns. This principle of liquid loading is illustrated in fig. 489.

In order to account for the very high frequency (20,000 to 30,000 c.p.s.) of the auditory strings at the base of the cochlea, one must suppose that the fibers in this situation are under a tension which, to opponents of the resonance theory, has seemed incredibly high. The length of the shortest basilar fiber is in the neighborhood of 0.16 mm. Such a fiber in order to be in tune with the highest audible frequency would need to be under a tension of nearly 4 tons per square inch (Beatty). Yet such a stretching force, enormous as it is, does not exceed the bounds of possibility when the strength of other biological materials is considered. A human hair, for example, can sustain a stress of 9 tons per square inch, a spider's thread, 12 tons per square inch and silkworm gut, 32 tons per square inch.

The basilar fibers are embedded in a homogeneous ground substance which by binding them into a continuous structure prevents them from vibrating separately; for this reason it would seem that they could not act as a series of resonators. This apparently insuperable objection to the resonance theory has been met by the conception of *maximum stimulation* advanced by Gray. For example, a sound sets into vibration not only those basilar fibers which are in tune with it, but also, though less forcibly, those for a variable distance on either side. This assumption is in agreement with observations upon pitch perception after auditory fatigue (p. 1028). It follows that there will be a central fiber or small group of fibers which vibrates maximally and other "out of tune" fibers which vibrate submaximally, the amplitude

of vibration decreasing progressively with the distance from the "in tune" or central resonators. Only those vibrations of maximal amplitude, it is claimed, lead to effective stimulation of the nerve endings. This concept of maximal stimulation is not merely an ingenious hypothesis, for the same principle appears to be the basis of cutaneous localization. When a pointed object is pressed upon the skin, e.g., on the finger tip, the sensation is restricted to a single small area; even with deep pressure one feels only a sharp point. Yet the skin for an area of several square millimeters surrounding the point of maximal stimulation is deformed sufficiently to arouse a definite sensation were the stronger stimulus absent.

It is also pointed out by Wilkinson that in order for the liquid columns to load the membrane in the manner described, it is necessary that the



We are therefore justified in accepting a "place" theory of pitch appreciation. There is a formidable array of evidence for the belief that the localizing mechanism comprises the fibers of the basilar membrane acting as a graduated system of resonators. The projection of the organ of Corti to the primary auditory center (p. 1025) and to the cerebral cortex with the preservation of a spacial arrangement also speaks for a place theory.

Observations and experimental results bearing upon the questions discussed in this section will be briefly cited (see also p. 1039).

(1) *The structure of the cochlea.* It is scarcely reasonable to regard the design of the cochlea, which upon close examination appears to be so admirably adapted to the selective reception of vibration frequencies, as being quite without meaning. Surely a much simpler mechanism would suffice for the stimulation of the nerve endings were the analysis of sound undertaken by the cerebral centers.

(2) A change in the form of a sound wave caused by simply altering the phases of the combined waves in relation to one another does not alter the pitch or quality of the sound. This fact alone is strongly in favor of the resonance theory and the results of an ingenious experiment performed by Hartridge lend further support. The phase of a tone sounded by a siren was altered by half a wave length (180°). The change in phase caused a brief period of silence (the "phase change beat"), the tone then returned and increased rapidly to its original intensity; there was no change in pitch. This phenomenon is taken as indicating the existence of resonators in the cochlea, being compared to the effect caused by a troop of men marching in step across a suspension bridge and then suddenly and in unison changing step. When the change in step is made, the bridge, which had been vibrating "in tune" with the tramping feet, is brought to rest for an instant, since the steps are now out of phase with its vibrations. But after this momentary period of "silence" the structure again picks up the rhythm, its motions soon reaching their previous amplitude.

(3) *The correlation of lesions localized to definite cochlear levels with loss of hearing over limited ranges of pitch.* (a) Boilermakers and others who work amidst loud, clanging sounds sometimes become deaf to tones of the same pitch as that of the noise, though retaining their hearing over other parts of the scale. Degenerative changes are found in that part of the basilar membrane which in accordance with the "place" theory corresponds to the range of the deafness. (b) Crowe and his associates examined *post mortem* the internal ears of 79 subjects of high tone deafness. Three-quarters of these showed atrophy of the organ

of Corti in the basal turn, or of the nerves supplying this part of the cochlea. These changes were much more extensive and severe than any found in the ears of 200 subjects with normal hearing. (c) "Islands" of hearing can sometimes be demonstrated in persons congenitally deaf to all other tones. It is impossible to account for such a phenomenon by any theory which attributes sound analysis to the cerebral cortex. It is inconceivable that the brain can perceive one set of impulse frequencies but fails in respect to all others, or that the basilar membrane vibrates as a whole to certain small ranges of vibration frequencies, as the telephone theory demands, but is unresponsive to those higher or lower in the scale. (d) The experiments of Witmarch and later of Yoshii and other investigators afford important evidence of some mechanism whereby sound vibrations are localized upon the basilar membrane according to their frequencies. Guinea-pigs were exposed over long periods to loud sounds of constant pitch. When the stimulating tone was of high frequency histological examination of the cochlea after death revealed degenerative changes in the organ of Corti of the basal turn, tones of medium pitch resulted in similar changes in the middle turn; structural changes at the apex were not produced, however, by tones of low pitch. Pavlov has shown, however, by the conditioned reflex method that destruction of the upper part of the cochlea in the dog causes deafness to frequencies below 600 c.p.s. (see footnote, p. 915). (e) Davis and Derbyshire and associates have recently investigated the effects of prolonged stimulation upon the labyrinth of guinea-pigs and upon the threshold of the electrical response of the cochlea. It was found that exposure for 75 days to frequencies of from 600 to 800 c.p.s. and intensities of from 60 to 95 decibels occasionally produced slight wide-spread cochlear damage and a corresponding rise in the threshold of the cochlear response. However, exposure to tones of 2500 c.p.s. and intensities of about 100 decibels for 40 days or so caused more or less extensive damage of the external hair cells of the organ of Corti in the middle part of the second turn of the cochlea and a corresponding rise in the threshold of the cochlear response, the highest threshold being for tones of 1200 c.p.s. In previous experiments it was shown by these observers that the cochlear response was a reliable index of auditory function, for its threshold was found to agree with that as determined by the method of conditioned reflexes. (f) Stevens, Davis and Lurie recorded the electrical response before and after drilling through the cochlear wall at different levels and damaging the organ of Corti. Good correlations were obtained between the levels of the lesions and the changes in threshold of the cochlear responses at corresponding frequencies. The diagram shown in fig. 490 was drawn from the results of these experiments.

THE BASIS FOR THE PERCEPTION OF LOUDNESS.

We have seen in considering the sense organs that the frequency of the impulses discharged along the individual nerve fibers, and probably also in some instances at least the number of functioning fibers, are the factors determining the intensity of the resulting sensation (p. 808). The loudness of a sound is now also believed to be dependent upon the frequency of the impulses in the individual nerve fiber and, but to a more important extent, upon the total number of active fibers. With a

sound of low intensity a narrow section of the basilar membrane tuned to a particular wave frequency is set into vibration and relatively few fibers are stimulated, whereas a loud sound sets in motion the basilar membrane on either side of this region of maximum vibration and a much larger number of fibers is stimulated. Thus, to quote Hallowell Davis “—pitch is a function of *where*, while intensity is a function both of *how much* of the basilar membrane is disturbed and of an increase in the rate of discharge of many of the activated fibers.”

CHAPTER LXXX

THE EUSTACHIAN TUBE. DEAFNESS. HEARING TESTS. THE HARMFUL EFFECTS OF NOISE

THE FUNCTION OF THE EUSTACHIAN TUBE.
THE EFFECTS OF OCCLUSION. The Eustachian tube affords the only means whereby the pressure of air within the middle ear can be equalized with that of the atmosphere. The pharyngeal orifice of the tube is closed at ordinary times, but opens during swallowing, yawning or when a high pressure is created in the nasopharynx, as by blowing the nose or making a forced expiration with the nostrils and mouth closed (Valsalva's experiment). During swallowing the orifice is opened by the contraction of small muscles—the *salpingopharyngeus* and *dilator tubae*—attached to its margins. The pressure within the tympanum may be raised above atmospheric pressure by the accumulation of inflammatory exudate, or become subatmospheric as a result of occlusion of the Eustachian tube. In the latter event air is gradually absorbed from the middle ear into the blood stream (see p. 370) and the partial vacuum thus created causes retraction of the drum membrane. The inward displacement of the membrane may be so great as to bring it into contact with the inner wall (promontory) of the tympanum, the cavity being almost obliterated. Deafness results, which is relieved by catheterization of the Eustachian tube or by inflating the ear by means of a Politzer bag, and thus equalizing the pressure on the two sides of the membrane. Temporary occlusion of the tube caused by swelling of the mucous lining is not an uncommon occurrence during an ordinary cold. A sensation of fullness in the ears is experienced, and usually some loss of hearing which is quickly relieved, as a rule, by swallowing or by blowing the nose and thus forcing air up the Eustachian tube. The latter practice is decidedly risky since it is likely to force infective material into the ear and cause acute inflammation.

The tympanic membrane is very sensitive to any difference in pressure on its two surfaces, and during rapid changes in altitude, as in aeroplane ascents and descents, annoying aural effects may be produced. In experiments reported by Armstrong and Heim, bulging of the membrane accompanied by a sensation of fullness occurred when the atmospheric pressure was reduced by an amount corresponding to an altitude of from 100 to 180 feet. When the reduction in pressure

amounted to 15 mm. Hg, which corresponds to an elevation of 500 feet above sea level, a distinct "click" was felt in the ear as the drum membrane snapped back into its normal position. These effects were due to the higher pressure in the tympanum forcing the Eustachian tube and thus equalizing the pressure on the two sides of the membrane. With further progressive reduction in atmospheric pressure a similar sequence of events was observed, except that the successive "clicks" occurred with a reduction in outside pressure of only 11.4 mm. Hg. This is taken to indicate that the pressures within and without the tympanum are not fully equalized at these altitudes, but that, though the Eustachian tube is forced open at an excess pressure of 15 mm. Hg in the middle ear, closure of the tube occurs while the inside pressure is still 36 mm. Hg above that of the atmosphere.

The results of raising the outside pressure above that in the middle ear, as in aeroplane descents, are quite different. The Eustachian tube acts like a valve, remaining firmly closed against any degree of external pressure. Up to a pressure of from 80 to 90 mm. Hg, the tube can be opened by swallowing, but at pressures greater than this the walls of the lower part of the tube are collapsed and held so firmly in this position by the partial vacuum in the middle ear that the dilator muscles are powerless to open it. Rupture of the drum membrane which, according to these observers, is accompanied by severe piercing pain, a loud explosive report in the ear and a sensation of being struck on the side of the head, occurs when the difference in atmospheric pressure and the pressure in the middle ear is from 100 to 500 mm. Hg. Nausea, vertigo and general shock are experienced. A pressure difference great enough to rupture the drum membrane in a conscious person is unlikely to occur unless the descent is very rapid (4000 feet per minute) because, even though there is no sensation to give warning of the increased pressure upon the ear drums, most persons swallow automatically every minute or so. Rupture of the membrane might easily occur, however, during sleep, in an unconscious patient in a hospital plane, or in a person with an occluded Eustachian tube.

DEAFNESS. Defective hearing may result from disease or abnormality affecting any part of the auditory mechanism. The transmission of sound to the internal ear may be interfered with as a result of some obstruction in the external auditory meatus, of failure of the Eustachian tube to maintain communication between the pharynx and the

middle ear, or of some disease or defect of the middle ear itself. Loss of hearing resulting from any of these causes is termed *transmission* or *conductive deafness*. Deafness due to loss of function from whatever cause of the receptor organs of the internal ear or of the auditory nerve is termed *perceptive deafness*, and that resulting from a lesion of the auditory pathways or of the auditory center is called *central deafness*.

Transmission deafness. Wax or a foreign body in the external auditory meatus or some developmental abnormality of the external ear may, by shielding the ear drum from the sound, cause deafness which, of course, varies in severity with the degree to which the meatus is obstructed. Deafness, usually of a temporary nature, commonly results from acute inflammation of the middle ear—*acute otitis media*—which is caused in the great majority of instances by the passage of infective material from the nasopharynx along the Eustachian tube during an ordinary cold, influenza or sore throat. During the acute stage of otitis media the ear becomes filled with fluid and is very painful; the accumulation of fluid raises the pressure within the tympanum and bulges the ear drum outwards. The inflammation may progress to pus formation which, if the condition is left to itself, is followed by perforation or rupture of the drum membrane. The surgeon endeavors to prevent rupture by making an incision at a dependent point so as to provide free drainage. The incision soon heals, leaving, as a rule, little or no loss of hearing.

Chronic or subacute otitis media causes progressive impairment of hearing due to fibrous adhesions which limit the movements of the ossicles, ankylosis of the incudomalleolar joint, or fixation of the base of the stapes in the oval window. Other factors which may be responsible for the loss of hearing are thickening of the drum membrane and occlusion of the Eustachian tube. In chronic middle ear disease the subject as a rule suffers a greater degree of hearing loss in the lower and middle tones of the scale; in perceptive deafness hearing is impaired mainly for the higher frequencies.

Otosclerosis is a chronic ear affection associated with progressive loss of hearing, especially for low tones. The deafness is due to osseous changes which commence in the outer wall of the labyrinth, particularly around the margins of the oval window. Limitation of movement of the base of the stapes results, the ossicle ultimately becoming fixed in the oval window. The pathological process commences with absorption of bone; this is followed by osseous overgrowth, the new formation having the structure of osteoid tissue containing wide spaces filled with connective tissue, rather than of true bone. Osteoblasts are numerous. The disease extends inwards, involving the bony labyrinth; degeneration of the hair cells of the organ of Corti is

found in most instances. Several theories have been proposed to account for otosclerosis, namely, that it is due to a disturbance of calcium metabolism associated with parathyroid dysfunction, that it is caused by infection following inflammation of the middle ear, or that it is a reaction set up by diminished blood supply to the osseous labyrinth caused by vascular sclerosis. Little evidence can be cited in support of any of these theories. The disease shows a familial tendency.

When the footplate of the stapes is rigidly fixed in the oval window the function of transmitting air-borne vibrations to the perilymph devolves upon the round window. The membrane here must then vibrate in sections which move in opposite phases—as one part of the membrane moves in the other moves out. The amplitude of the movements is minimal. For the reason mentioned on page 1035 no appreciable movement of the membrane as a whole is possible. An operation devised by Holmgren and modified by Sourdille, by Lempert and by others, with the view of increasing the amplitude of vibration of the basilar membrane in otosclerosis has so far yielded most encouraging results. The surgical procedure consists in drilling through the osseous wall of a horizontal semicircular canal and covering the gap with a cutaneo-membranous flap reflected from the depth of the external auditory canal and the adjacent portion of the tympanic membrane. By thus providing an artificial second window, pressure variations incident upon the round window are readily transmitted through the internal ear.

Perceptive deafness may result from injury which causes detachment of the sensory cells of the organ of Corti, from inflammatory conditions of the labyrinth, from degeneration of the sensory cells following prolonged and strong stimulation (p. 1040) or from injury or disease of the auditory nerve, such as fracture of the base of the skull or tumor in the region of the cerebello-pontine angle. A tumor in the latter situation is likely to involve the vestibular division of the nerve as well. Deafness is not infrequently due to a developmental defect of the internal ear, the degree of deafness varying in different instances from a slight impairment to deaf-mutism. The latter condition, though frequently congenital, may result from some disease of the ear during infancy which leads to complete loss of hearing. In deaf-mutes the semicircular canals are not infrequently undeveloped as well as the cochlear part of the labyrinth; in such persons the responses to the ordinary tests of vestibular function (e.g., rotation, p. 839) are absent.

Central deafness. A unilateral lesion of the lower part of the auditory pathway, e.g., in the medulla, before any of the fibers of the cochlear division have crossed to the opposite side of the brain stem causes loss of hearing in the ear on the side of the lesion. But some fibers ascend uncrossed, thus each ear is bilaterally represented in the cerebral cortex. A uni-

lateral lesion of the auditory pathways anywhere above their decussation therefore causes little or no impairment of hearing, and any which may result affects both ears. Slight if any loss of hearing follows the complete surgical removal of one temporal lobe.

Paracusis Willisii is the term given to the curious phenomenon first described by Willis (1630), that a deaf person hears better in noisy surroundings, as in traffic, trains, etc. There are two main forms—false and true. *False paracusis* is common and easily explained upon the basis of masking (p. 1031). *True paracusis* is rare; there is a real increase in auditory acuity, for it is not only conversation which is heard better but a sound kept at a constant intensity is also rendered more distinct by the presence of noise. The phenomenon has not received a satisfactory explanation. Some believe that it occurs only when there is some stiffness in the articulations of the ossicles. The noise vibrations, it is thought, by “shaking up” the joints render the ossicular chain more efficient in transmitting other weaker sound waves. Other suggestions are that the noise increases the blood supply to the cochlea, or that through the jarring effect of the vibrations the auditory nerve is rendered more irritable.

HEARING TESTS

Disease confined to the middle ear affects the transmission of air-conducted sounds only; conduction through the bones of the skull is not interfered with. When, for example, a vibrating tuning-fork is held to the ear of a subject with middle ear disease, he may fail to hear it, but when the shaft of the fork is pressed against his skull (e.g., the mastoid process) the sound is heard at least as well by him as by one with normal hearing. In deafness due to disease of the internal ear or of the auditory pathway the perception of bone-conducted sounds as well as those transmitted through the middle ear is impaired.

The following tests are employed to distinguish perceptive from transmission deafness.

Weber's test. The tone of a tuning-fork applied to the forehead of a person with normal hearing is referred to the mid-line. In unilateral middle ear deafness the sound is localized in the diseased ear, whereas in deafness due to disease of the labyrinth or of the auditory nerve of one side it is heard best or only in the normal ear. This apparently arbitrary result is to be explained upon the basis of masking. In unilateral middle ear deafness, the cochlea of the affected side is shielded from air-borne sounds as a result of defective transmission, whereas on the normal side the tone is masked; it follows that in a perfectly silent room the sound would not be localized to either side. A person with normal hearing ordinarily hears more acutely in one ear if the opposite ear is closed by the finger, but in

perfectly silent surroundings the hearing in one ear is not improved by blocking the other. *Rinne's test.* Each ear is tested separately, the auditory meatus of the opposite side being blocked by the observer's finger. A vibrating tuning-fork is applied to the mastoid process; when the sound is no longer audible to the patient the fork is brought close to the corresponding auditory meatus. The subject of middle ear deafness does not hear the sound after it has ceased to be heard through the bone; the test is then said to be negative (*Rinne negative*). A person with a normal middle ear hears the sound for a short time through the air after it is inaudible through bone (*Rinne positive*). *Schwabach's test* consists of the accurate measurement in seconds of the time interval during which the sound is heard through bone (bone-conduction test) or through the air (air-conduction test). Or the length of the interval in each instance may be compared with that during which it is heard by the examiner. For example, at the moment that the patient no longer hears the sound through bone, the fork is placed upon the mastoid process of the examiner; or after the patient ceases to hear the fork through air it is brought to the examiner's auditory meatus. In both forms of the test the length of time during which the examiner hears the sound after it is inaudible to the patient gives a measure of the hearing loss. A patient with middle ear deafness hears the sound by bone-conduction for a longer time than the examiner, in whose ear the tone of the fork is masked by room noise. In a perfectly silent room, of course, the patient's hearing through bone would be no better than the examiner's. In perceptive deafness the tone is heard through bone for a shorter time than the normal.

TESTS OF AUDITORY ACUITY. The foregoing tests are employed in determining the part of the auditory apparatus affected. Other test sounds, such as the observer's voice (whisper), the click of a coin or the tick of a watch, are used in determining the threshold of hearing. Since a sound varies inversely as the square of the distance from its source, these tests have no meaning unless the maximum distance at which the sound can be heard by the subject is known and compared with that which can be heard by the average normal ear. The subject's hearing is then expressed as a fraction of the normal—the maximum distance at which the sound is just audible to the patient over that at which it is heard by a person with average hearing under the same conditions. In quiet surroundings a good watch is heard by the normal ear at a distance of about 3 feet and words spoken in an ordinary whisper at about 30 feet. These tests are admittedly rough and give little information of the threshold of hearing at different pitches. In such a determination a series of tuning-forks may be used. The test fork is given a “standard” blow and then held as close to the ear as possible with the flat surface facing the meatus. The time, t , in seconds from the moment that the blow is struck until the sound becomes inaudible to the patient,

is compared with the normal time, t_0 . The degree of hearing loss is then derived from the difference, $t_0 - t$.

The audiometer. Within recent years an instrument known as the *audiometer* has been introduced for the rapid and more precise testing of auditory function. The apparatus is designed upon principles similar to those used in radio sets, the test tones being generated electrically and conveyed by wires to a receiver applied to the patient's ear. The tone is varied in intensity or pitch as required by means of dials upon the front of the instrument. The intensity (in decibels above the audible threshold) or the pitch is indicated directly on the respective dial. In one form of the instrument compound tones covering the range of speech frequencies are employed; another type replaces the tuning-fork test, a series of pure tones with frequencies ranging from 64 c.p.s. to 8000 c.p.s. being employed. In a third type speech sounds from a gramophone record are led through the instrument and then to a receiver applied to the patient's ear. The results of the test are plotted as shown in fig. 491. Such a record is called an *audiogram*. Special receivers have also been designed for bone conduction tests. Alternating electrical currents are transformed into mechanical vibrations applied to the skull.

THE HARMFUL EFFECTS OF NOISE. Noise is recognized as an annoyance and a general nuisance but is not, as a rule, classed as an influence detrimental to health or efficiency. Yet there is no question that, quite apart from the injurious effects of prolonged and loud sounds upon the internal ear (p. 1045) or of loud reports upon the ear drum and mechanism of the middle ear, noisy surroundings can lead to mental irritability, "nervous strain" and increased expenditure of energy. Noise reduces efficiency and accuracy in the performance of manual work, e.g., mail sorting, typesetting, operating factory machines, etc., which demand some degree of attention. The distracting effect of noise upon mental tasks and its interference with restful sleep are too obvious to require comment. That it has a deleterious influence upon persons seriously ill is unquestionable; it is therefore reasonable to believe that, though a healthy person appears to endure almost any degree of noise without immediate detriment to his well-being, he is not immune to its ill effects. There are many observations to the contrary. Watkyn-Thomas and Yates cite the case of an elderly office

worker who was moved from a quiet to a noisy environment. Although his disposition had previously been kindly and courteous it became altered in an unaccountable way; not until he took up his quarters again in a quiet room did his good nature return. In factory workers the accuracy of certain types of operation may be reduced by from 50 to 60 per cent by noise. In a telephone exchange wrong numbers were observed to decrease by 42 per cent when the noise was lowered

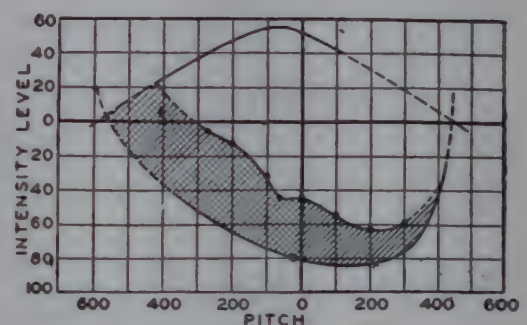
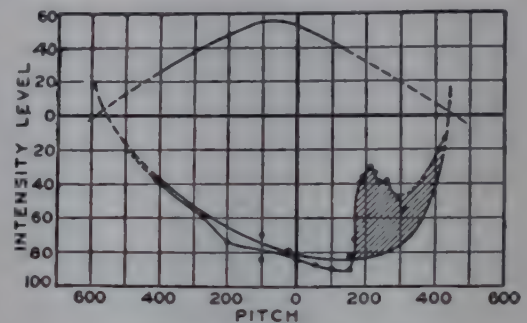


FIG. 491.

from 5 to 3.5 bels. It has also been shown that noise increases the oxygen consumption for a given piece of light work, e.g., typing, by from 20 to 25 per cent. The extra energy expenditure is due apparently to increased action of the heart, more rapid respiratory rate and greater muscular tone. In animals, e.g., cats, dogs, rabbits and frogs, such reactions, as well as a rise of blood pressure, can be shown to result from continuous noise or from a sudden loud sound. Beatty points out that there are only three things which evoke a fear reaction in very young infants, namely, letting them fall even a short distance through the air, holding their arms to their sides, or a *sudden loud noise*.

CHAPTER LXXXI

THE CHEMICAL SENSES

TASTE

Taste and smell are chemical senses, that is to say, the receptors (chemoreceptors) for these senses respond adequately to chemical stimuli. In order, therefore, for a substance to arouse a sensation of taste it must be dissolved—either taken in solution or dissolved in the saliva; a solid taken into a perfectly dry mouth is tasteless. For this reason the organs of taste or *taste buds* are present only upon a moist surface, being confined to the mouth region of all air-breathing vertebrates, but may be anywhere upon the body surface of aquatic forms.

THE ORGANS OF TASTE. The taste buds of man are mainly situated on the tongue but a few are also found in the mucous membrane covering the soft palate, fauces, epiglottis and the region of the arytenoid cartilages. Taste buds are more widely distributed in children, and are especially plentiful over the anterior part of the tongue. In the adult they are much fewer at the tip of the tongue and are almost absent from the middle third. In fishes the skin of the general body surface is plentifully supplied with taste receptors, and in the catfish and certain other species of fish they are contained in the filiform processes known as barbules projecting from the snout and angles of the mouth. In insects (flies, bees) taste receptors are located at the end of the proboscis and upon the tarsal segments of the legs.

The mucosa of the human tongue is studded with large numbers of small elevations—the *lingual papillae*—caused by projections of the corium. The papillae are of three main types, filiform, fungiform and vallate. The *filiform papillae* are very minute conical structures covering the anterior two-thirds or so of the dorsal surface of the tongue. They are arranged in rows running roughly parallel with the rows of vallate papillae. The *fungiform papillae* are considerably larger than the preceding type, round in shape and situated mainly at the tip and edges of the tongue. The *vallate papillae* are much larger and become especially prominent posteriorly where from six to twelve are arranged conspicuously in the form of a V with its limbs open anteriorly. A vallate papilla consists of a central round elevation with perpendicular sides and surrounded by a sulcus; the taste buds are situated in the mucosa forming the walls of this circular trench. The filiform papillae rarely contain taste buds, but each fungiform papilla usually holds from 8 to 10 embedded in the epithelium covering its free surface.

A section of a taste bud is shown in figure 492. It measures about 70μ long and 50μ broad, and lies with

its long axis perpendicular to the epithelial surface. It consists of groups of *supporting cells* (*peripheral supporting cells*) shaped somewhat like the sections of a musk melon and arranged side by side to enclose a small oval chamber which opens superficially through a circular gap—the *inner taste pore*—bounded by the converging ends of the supporting cells. The inner taste pore usually leads into a short canal which opens in turn through the *outer taste pore* upon the surface of the tongue. The cavity of the taste bud is occupied by other supporting cells (*central supporting cells*) in the intervals between which the taste receptors (*taste cells*) are lodged. The taste cell is spindle-shaped and provided with a fine hair-like process which projects through the inner taste pore into the short canal men-

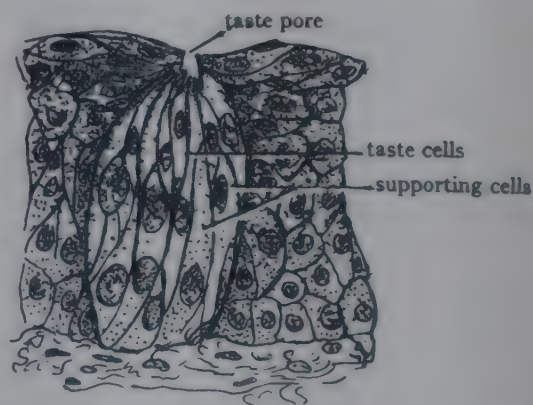


FIG. 492. Vertical section through a taste bud.

tioned above. The taste bud contains a variable number of these sensory cells, usually from 5 to 18. Nerve fibers after losing their medullary sheaths penetrate the bud and arborize upon the surface of the taste cells.

The chief nerves of taste are the *chorda tympani* branch of the facial nerve and the *glossopharyngeal nerve* (see fig. 183, p. 418). The former supplies the taste buds over the anterior two-thirds of the tongue, the latter is distributed to the posterior third. The *vagus nerve* innervates the few taste buds which are present in the region of the epiglottis and arytenoid cartilages. The *trigeminal nerve* mediates common chemical sense (p. 1058) and sensations of touch, temperature and pressure (common sensibility) from the entire buccal mucosa; it does not contain taste fibers. Cushing observed, for example, that removal of the semilunar ganglion did not cause any permanent loss of taste (p. 858). Section of the nerves of taste in animals is followed by degeneration and gradual disappearance of the taste buds. Olmsted has shown in experiments upon the catfish that taste buds reappear upon regeneration of the nerve fibers. The latter evidently exert a formative influence, possibly

through the medium of a chemical substance, upon the development of the taste organs.

The central connections of the nerves of taste are described on pages 859-861 and 895.

THE SENSATIONS OF TASTE

There are four *simple, primary* or *fundamental* tastes—*sweet, sour (acid), salty* and *bitter*. Two others are sometimes added, namely, *alkaline* and *metallic*.¹ The various other tastes which we experience are (a) blends of two or more of the primary sensations or (b) combinations of the latter with sensations aroused by the stimulation of the nerves of common sensibility. For example, ginger is recognized not only by its taste (i.e., through impulses from the taste buds), but also by the burning sensation caused by the excitation of the ordinary sensory nerves of the mouth and also, we may add, by its odor. Many other substances, such as fats and oils and pungent condiments, are “felt” as well as tasted.

Many of the finer flavors are in reality sensations of smell, and olfaction enters very largely into many of the sensations which we generally class as tastes. For this reason when the nose is held or the nasal passages blocked, as during an ordinary cold, our sense of taste seems blunted. It may then be impossible if two foods are of the same consistency to distinguish between them; thus an apple and a pear, or a turnip and a potato, taste alike. On the other hand, certain substances which we think that we detect by smell are actually tasted. The sweetish smell of chloroform is an example; the vapor reaches the taste buds in the inspired air.

The four primary gustatory sensations are not aroused with equal intensity over all parts of the tongue. Apparently there is a functionally distinct type of receptor for each primary taste, and the distribution of each type is not uniform over the lingual mucosa. End organs sensitive to sweet and salty materials are most plentiful at the tip, those responsive to acid are distributed mainly along the margins, while those aroused by bitter substances are towards the base of the tongue and in the region of the epiglottis. These facts are recognized generally in practice, for one would no

more think of sipping beer than he would of gulping a glass of wine, and a child prefers to lick rather than munch a stick of candy. Some substances stimulate two types of taste bud. For example, *sodium salicylate, rhamnose* and *para-brom-benzoic-sulphinide*, a substance related to saccharine, give a sweet taste when applied to the tip of the tongue but when swallowed, and thus brought into contact with the vallate papillae, taste bitter. *Ortho-benzyl-benzoate*, on the other hand, gives a bitter followed by a sweet taste. *Magnesium* and *sodium sulphates* are salty-bitter, causing a salty taste at the tip of the tongue and a bitter taste at the base. When the papillae are

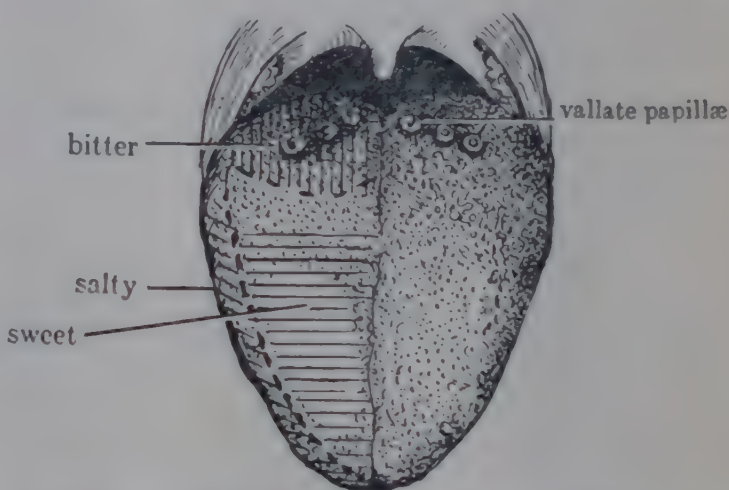


FIG. 493. Showing distribution of primary taste sensations on one side of the tongue.

explored individually with different sapid substances it is found that the filiform type are insensitive. Of the fungiform papillae, some respond to both sweet and salty compounds, others to acid and sweet and others again to bitter and acid. A few respond to all four types of stimulus. These results indicate the existence of functionally distinct types of taste receptors and that different types are present in the same fungiform papilla. Only taste buds responsive to bitter substances are present in the vallate papillae (fig. 493).

Gustatory impulses in single nerve fibers aroused by the application of chemicals to the tongue of the cat have been recorded by Pfaffman. Only three types of active fiber were identified, (a) those which responded to acid, (b) those which responded to acid and salt, and (c) those which responded to acid and quinine. No difference was observed in the character of the impulses which might serve to distinguish the type of stimulus employed. Such a finding is in accord with what we know of other sense organs, namely, that the quality of sensation is determined by the central connections of the nerve

¹ Opinions differ as to the nature of these two sensations, most investigators contending that the former is a compound sensation, resulting from the excitation of several types of end organs, including those for sweetness and for touch. Similarly, the metallic taste caused by the salts of heavy metals, copper, silver, mercury, etc., is believed to be a complex of sour and sweet. Some maintain indeed that it is due chiefly to the stimulation of olfactory receptors.

fiber, that is, upon the part of the brain where the impulses set up in the receptor organ by an adequate stimulus, are delivered.

The sense of taste may be aroused by substances reaching the taste buds in the blood stream. Thus the intravenous injection of histamine causes a metallic taste, glucinum a sweet taste, and in jaundice a bitter taste may be experienced as a result of the high concentrations of biliary constituents in the blood.

TASTE SENSATIONS AND CHEMICAL CONSTITUTION. The *sweet* taste is associated predominantly with organic compounds, especially the *sugars* (e.g., sucrose, maltose, glucose, etc.) certain *polysaccharides*, the *alcohols*, *aldehydes* and *ketones* of the aliphatic series, and *saccharine*, *dulcine* and *chloroform*. But certain inorganic substances, such as *lead acetate* (sugar of lead) and *alkalis* in high dilution, are also sweet to the taste.

Several attempts have been made to relate the sweet taste to chemical constitution. Oertly and Myers, for example, from a study of a large number of sweet organic compounds have proposed the theory that every sweet molecule contains two particular types of radical or an atom upon which the sweet taste depends. One of these they call a *glucophore*, the other an *auxogluc*. A glucophore makes a given compound a potential tastestuff; if it is bound to an auxogluc a sweet compound is produced. Some six glucophores and nine auxoglucs have been identified; four of each are listed in the following table.

Glucophores	Auxoglucs
(1) —CO—CHOH—(H)	(1) H
(2) $\text{CO}_2\text{H} \cdot \text{CHNH}_2\text{—}$	(2) CH_3CH_2
(3) $\text{CH}_2\text{OH} \cdot \text{CHOH—}$	(3) CH_2OH
(4) $\text{CH}_2\text{ONO}_2\text{—}$	(4) $\text{CH}_2\text{OH CHO}$

Thus the hexoses contain the glucophore (1) and the auxogluc (4), glycerol the glucophore (2) and the auxogluc (3), and amino-acetic acid the glucophore (2) and the auxogluc (1).

The *salty* taste is evoked primarily by inorganic compounds, notably the *chlorides* of *sodium*, *potassium*, *magnesium*, *ammonium* and *lithium*, by certain *sulphates*, *bromides* and *iodides* and by *sodium* and *potassium nitrates*. The saline taste of such compounds is attributed to the anions (Cl , Br , I , SO_4 and NO_3), a conclusion arrived at from a comparison of their tastes when in high dilution with that of an equally weak solution of sodium acetate. For example, a 0.04 molar solution of NaCl , of KCl or of LiCl has a slightly

salty taste, whereas sodium acetate in equal or somewhat lower dilution is tasteless or at least is not salty. Similarly sodium bromide, iodide or nitrate loses its saline taste at a much higher dilution than does the acetate. Of the halogens the dilution at which the salty taste is just perceptible is highest for the chloride, next for the bromide and lowest for the iodide ion. The saline taste is not confined to inorganic compounds. Certain organic compounds, such as the *hydrochlorides* of *monomethylamine* and *diethylamine* also possess this property.

The *sour* taste is produced by acids or acid salts. It is generally agreed that the effective agent is the hydrogen ion. This statement would seem to be contradicted by the fact that solutions of certain organic acids, such as acetic, tartaric, citric, etc., are more acid to the taste than a solution of a mineral acid having a considerably greater hydrogen ion concentration. For example, the acid taste of a solution of acetic acid is about equal to one of HCl in a dilution one third as great. Yet as compared with the latter solution, the solution of HCl , since this acid is highly dissociated, is from 4 to 5 times as great. The greater effectiveness of acetic acid for a given H ion concentration is attributed to its greater power of penetrating the tissues, and therefore to its greater effectiveness in raising the hydrogen ion concentration within the taste buds. The *astringent* taste is attributed to acid in very high dilution, that is, to a greatly attenuated sensation of sourness.

The *bitter* taste, like sweetness, is associated chiefly with organic compounds, especially the *alkaloids* (*quinine*, *strychnine*, *morphine*, etc.) and certain *glucosides*. *Picric acid*, *dextromanose* and *bile salts* are among the other bitter organic compounds. Of inorganic substances with a bitter taste are *magnesium*, *ammonium*, and *calcium salts*. The bitterness of these salts is due to the cation. A slight change in the chemical constitution of a substance often alters its taste from bitter to sweet. Saccharine, for example, is intensely sweet, but some of its derivatives are bitter; dulcin is some 500 times sweeter than cane sugar yet *phenyl-thio-carbamide*, in which one oxygen atom in the dulcin molecule is replaced by a sulphur atom, is bitter to most persons. Phenyl-thio-carbamide is peculiar in that to 3 persons out of 10 it is tasteless. The taste deficiency ("taste blindness") in respect to this substance is hereditary, being transmitted as a Mendelian recessive.

Many organic compounds having a bitter taste contain NO_2 groups. If the molecule contains two such groups the compound is usually, though not necessarily, bitter; if three are present it is invariably so.

INADEQUATE STIMULI. Of agents other than chemical which are capable of evoking a sensation of taste by far the most effective is the electrical current. Electrical stimulation by means of the constant current, using a pair of electrodes placed upon the tongue causes, upon breaking the current, a metallic taste which persists for a little time. If one electrode is placed in contact with the surface of the tongue and the other upon some indifferent part of the body, a constant current during its passage causes an acid or alkaline taste, depending upon the direction of the current. If the lingual electrode is the anode an acid taste is experienced, whereas if the cathode is the stimulating electrode the taste is alkaline. Two factors, apparently, are concerned in the production of the acid or alkaline taste, namely, direct electrical stimulation of the taste cells and the production of H and OH ions at the anode and cathode, respectively, as a result of electrolysis of the buccal fluids. That a gustatory response can be produced by direct electrical stimulation is evident from the fact that it is more readily aroused by a rapidly alternating current, which has no appreciable electrolytic action, than by a direct current. Furthermore, when two persons are connected each to a pole of a battery and the circuit completed by bringing the tips of their tongues together, they experience different taste sensations, one acid the other alkaline. Now the two sets of taste buds must be exposed to the action of the same ions, the only condition of the experiment which is different in respect to the taste organs of the two persons is the direction of the current. The electrical taste evoked by a constant current is a rather complex sensation and cannot be described as purely acid or alkaline in quality. It frequently has a bitter metallic component which, as mentioned above, is usually the only taste caused by a single break shock. Very probably electrolytic products as well as the direct stimulating effect of the current are responsible for evoking the complex response. The gustatory sensation caused by a single shock is apparently due purely to direct electrical stimulation, since a current of such brief duration could not have any electrolytic action.

Thermal and mechanical types of stimulation may arouse faint sensations of taste but, as a rule, are ineffective.

Thresholds of the primary taste sensations. Minimum concentrations of the four main groups of sapid substances which will evoke the corresponding sensations are given in the following table.

<i>Sensation and substance</i>	<i>Concentration</i>
<i>Sweet</i> cane sugar.....	1 part in 200
dulcin.....	1 part in 100,200
α -antialdoxine	
perillaldehyde.....	1 part in 600,000
<i>Salty</i> , sodium chloride.....	1 part in 400
<i>Acid</i> , hydrochloric.....	1 part in 15,000
<i>Bitter</i> , quinine.....	1 part in 2,000,000
strychnine.....	1 part in 2,500,000

AFTER TASTE AND TASTE CONTRASTS. The sense of taste exhibits phenomena analogous to positive after images and successive and simultaneous contrast, which have been described for vision (p. 982). It is a familiar experience that the tastes of certain substances (e.g., quinine) "cling" to the tongue. But it is unlikely that the persistent taste is a true after sensation comparable with an after image; it is most probably due simply to the continued action of the stimulating agent which, having entered the taste pore, is removed with difficulty by the saliva or even by rinsing the mouth with water. On the contrary, the metallic taste which outlasts a single break shock is in all likelihood an example of the persistence of sensation.

Several observations exemplifying *successive contrast* can be cited. A sweet taste is enhanced by a preceding salt or bitter taste and vice versa. In the same way sour and sweet tastes intensify one another. Even distilled water tastes sweet after rinsing the mouth with a weak solution of sulphuric acid, and lemon juice seems much more acid following a sweet stimulus. Other examples which should probably be placed under the heading of successive contrast are the sweet taste which is experienced upon smoking a cigar or cigarette after washing out the mouth with a weak solution of copper sulphate, and the bitter taste caused by smoking if the tongue or buccal mucosa has been treated with a solution of silver nitrate. *Simultaneous contrast* is also demonstrable. For example, if one border of the tongue is rubbed with salt the sensitivity of the opposite border to a sweet stimulus is increased. This contrast effect must, of course, be of cerebral origin. Salt and acid also show simultaneous contrast, but the phenomenon cannot be demonstrated for the bitter taste.

The effects of drugs upon taste. Certain drugs have a selective action upon the taste sensations, abolishing some while leaving others unaffected. For example, after the application of a decoction of the leaves of *Gymnema sylvestre* to the tongue, sweet and bitter substances cannot be tasted, but saline and acid tastes are retained, and are only slightly if at all depressed. *Stovaine* acts similarly to gymnema but is less effective. *Cocaine* abolishes all taste as well as common sensibility,

the several sensations disappearing in the following order; pain, bitter, sweet, saline, acid and touch.

SMELL

THE OLFACTORY EPITHELIUM. The mucous membrane lining the greater part of the nasal cavity has no true olfactory function (see p. 1054). The olfactory receptors are confined to the nasal mucosa over a relatively small region—the *olfactory area*. This area comprises, on each side, the walls of a narrow niche (fig. 494) formed by the superior nasal concha, the upper part of the septum and the roof of the nose (cribriform plate of the ethmoid bone). The olfactory epithelium differs both in its gross appearance and

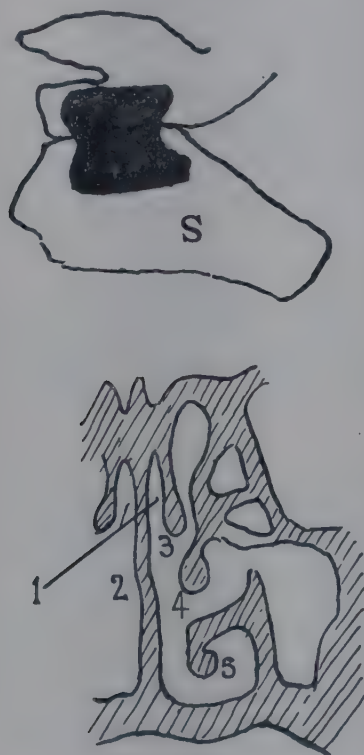


FIG. 494. Upper, human olfactory cleft opened by turning nasal septum (S) upward; black area represents olfactory epithelium. (Redrawn from Parker, after Read.) Lower, transverse section through human left nasal cavity. 1, olfactory cleft, 2, septum; 3, 4 and 5, superior, middle and inferior conchae.

histologically from the rest of the nasal mucosa. It is yellowish or brownish yellow in color; its total area, i.e., on both sides of the nose, is about 500 square millimeters.²

² The *vomero-nasal organ* (organ of Jacobson) is a short tubular structure which, though well developed in certain lower vertebrates, is rudimentary in primates. It can be identified in a vestigial form in infants but, though it may persist throughout life, it is commonly absent in the adult. When present it is situated in the lower anterior part of the nasal septum and opens into the cavity of the nose by a minute pore a short distance within the external nares. In the dog and cat it receives both olfactory and trigeminal fibers and contains epithelium similar to that of the olfactory area. The function of the vomero-nasal organ is not known with certainty but its general structure and innervation suggest very strongly that it is a subsidiary olfactory sense organ.

The olfactory epithelium is composed of three types of cell (a) supporting cells, (b) basal cells and (c) bipolar nerve cells. The *supporting cells* are of a very high columnar type with large oval nuclei. Superficially, they form a continuous epithelial surface, except for small round gaps between them through which the olfactory vesicles with their tufts of hairs project (see below). Their cytoplasm contains granules of a golden brown pigment to which the color of the olfactory epithelium is due. Proximally, the supporting cell tapers into a long slender process which extends as far as the lamina propria (fig. 495, A). The *basal cells* are squat conical structures which extend for only a short distance above the lamina propria. They are believed to develop into supporting cells, thus serving as a reserve from which the latter when destroyed can be replaced.

The *bipolar nerve cells* are the essential olfactory sense organs. Their two processes arise from opposite poles of the fusiform cell body, the dendrite from its superficial and the axon from its deep aspect. The dendrite is a long straight and relatively stout cylindrical process. It extends to the epithelial surface and projecting through one of the gaps between the supporting cells, expands slightly to form the *olfactory vesicle*. The latter contains from 6 to 8 granules each of which gives rise to a hairlike protoplasmic process. The axon of the bipolar cell proceeds centrally from the deep aspect of the perikaryon and after traversing the lamina propria, joins with the central processes of neighboring cells to form some 20 nerve strands—the *fila olfactoria* or *olfactory nerves*. The latter ascend in grooves in the ethmoid bone and, entering the skull through perforations in the cribriform plate of this bone, end within the *olfactory lobe (bulb)* by synapsing with dendrites of the *mitral cells* and *tufted cells* (fig. 495, B). The synapses form conspicuous spherical structures called the *olfactory glomeruli*. The axons of the mitral and tufted cells constitute the *olfactory tract*. Most of the fibers of the latter are continued into the *lateral olfactory stria* which conveys the impulses to the cortical center for smell (p. 896). The olfactory nerves are non-medullated, but possess a neurilemma. The lamina propria of the olfactory mucous membrane contains glands of the tubulo-alveolar type—the *glands of Bowman*. They secrete a serous fluid which bathes the epithelial surface, thus providing a solvent for odorous materials. The fluid is delivered by fine ducts which take a perpendicular course to the surface.

It will at once be recognized from the foregoing description that the end organs of smell differ from those of any other sense in that the cell body of the primary neuron is situated in the peripheral organ itself, and is stimulated directly without the intervention of a specialized receptor cell. No other sensory mechanism possesses both these features. Though the primary neuron of the visual pathway is situated in the retina, the stimulus is received by the rods and cones:

pain sensations are subserved by bare nerve endings, the cell bodies of the pain fibers are located in the posterior root ganglia. It is also important to remem-

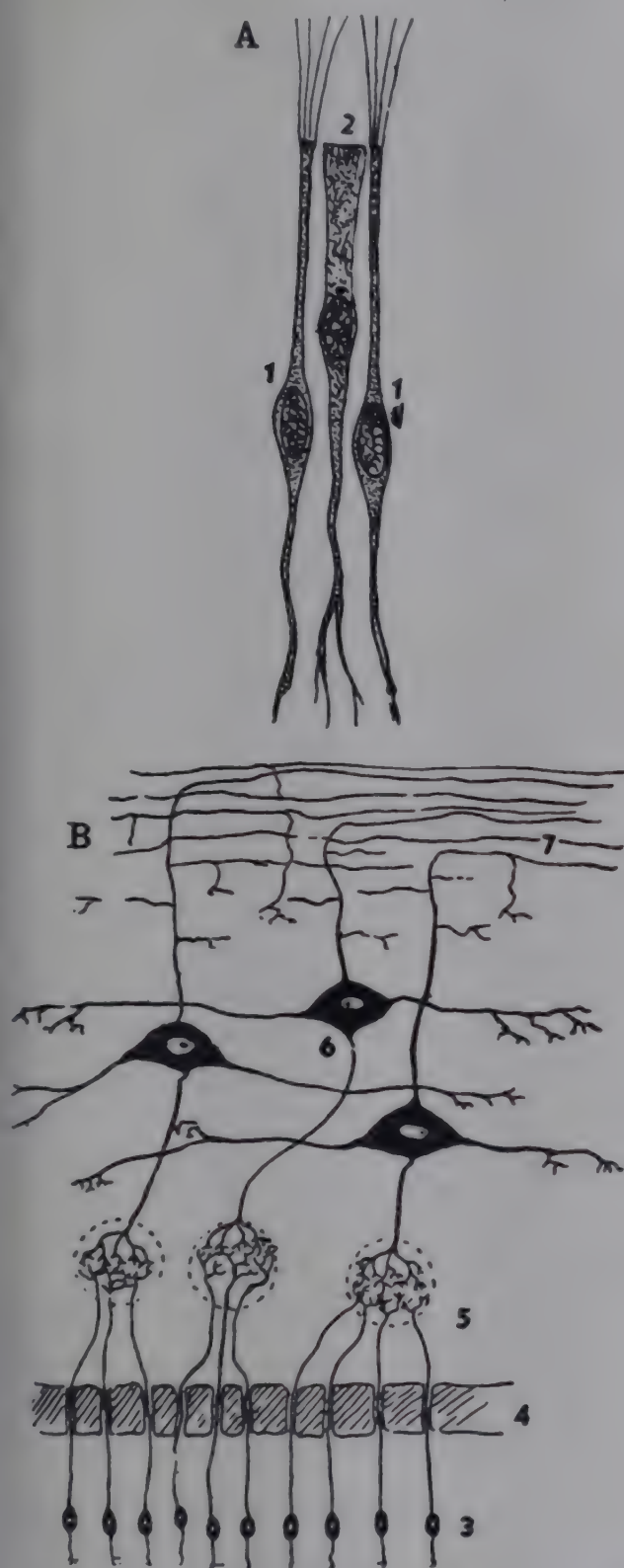


FIG. 495. A, cells from olfactory mucous membrane separated from one another and highly magnified. 1, olfactory receptors; 2, supporting cells. B, central connections of the olfactory nerves. 3, cells of olfactory mucous membrane; 4, olfactory nerve fibers piercing the floor of the skull to reach the olfactory bulb; 5, connections of olfactory nerves with processes of mitral cells in olfactory bulb; 6, mitral cells; 7, fibers passing into the olfactory tract.

of fluid. Furthermore, the sheaths of the olfactory nerves are continuous with the subarachnoid space. Experimental work indicates that the olfactory nerves constitute one pathway through which the virus of anterior poliomyelitis reaches the central nervous system. Shultz and Gebhardt have shown, for example, that monkeys are protected against the intranasal injection of poliomyelitis virus by a previous section of the olfactory nerves. Intranasal sprays, consisting of solutions of zinc sulphate and other substances have been employed in monkeys with the purpose of blocking these channels. The encouragement derived from the success of these experiments in protecting animals from the disease has led to the trial of similar measures in poliomyelitis epidemics, but unfortunately they do not appear to have any value in reducing the number of cases. It is very difficult, especially in children, to bring the solution into contact with the olfactory epithelium, and this is probably the reason that reliance cannot be placed upon intranasal spraying as a preventive. The recent experiments of C. G. Smith are enlightening. The olfactory areas of rats were treated with a 1 per cent solution of zinc sulphate and examined histologically at periods of from 2 days to 2 months thereafter. In animals so treated, destructive changes amounting even to sloughing of the entire olfactory epithelium were found, and in all cases the bipolar cells showed widespread degeneration. Regeneration of non-sensory cells (supporting and basal) subsequently occurred, but, of course, the nerve cells were not restored. It would appear from these experiments that zinc sulphate solution, if it is to be effective in protecting the intestinal pathway against the virus of poliomyelitis, must entail permanent loss of the sense of smell.

THE PHYSIOLOGY OF THE SENSE OF SMELL

OLFACTORY SENSATIONS. Smell is very closely allied to taste and has been aptly described as "taste at a distance." In many animals the sense of smell is almost incredibly acute, a relatively large part of the brain being given over to it. In the life of such macrosmatic animals the olfactory sense is of paramount importance, warning the animal of the approach of its enemies, guiding it in the quest for food and motivating the sex reflexes. Certain species of moth (e.g., great peacock and banded monk) are credited with a degree of olfactory acuity which seems almost mythical to microsmatic man, the female being able, it is claimed, to attract the male by the odor of its secretions from a distance of a mile or more. The olfactory organs of moths and most other insects are located in the antennae. Even man, in whom smell is a comparatively rudimentary sense, can detect certain substances (e.g., mer-

ber that here as nowhere else the nervous system is in direct contact with the external environment. The terminations of the dendrites of the olfactory cells, namely, the olfactory hairs, are covered only by a layer

captan and artificial musk) in a dilution of 1 part in several billion parts of air; smell is therefore much more acute than the sense of taste.

The adequate stimulus for the olfactory receptors, as for those of taste, is chemical.¹ An odorous material continuously emits particles of molecular size which reach the olfactory area through the air. Substances which pass readily into the gaseous state, such as turpentine, gasoline, the essential oils, etc., have strong odors, whereas non-volatile materials, e.g., the heavy metals, are inodorous. Arsenic, which ordinarily is odorless gives off a characteristic smell, however, when heated to a temperature at which it volatilizes, and Elsberg, Brewer and Levy found that the olfactory coefficients (p. 1056) of a number of odorous liquids vary directly with their boiling points. The niche forming the roof of the nose and which is lined by the olfactory epithelium, constitutes a blind pocket, from which the main air currents caused by the respiratory movements are excluded. Experiments upon the human cadaver have shown that the respired air does not come into direct contact with the olfactory area. A head was bisected in the median plane and the nasal septum replaced by glass. When smoke was forced back and forth through the nose by means of bellows, neither during the artificial inspiratory nor expiratory movement was the current observed to enter the olfactory region. The air flow takes a curved course, the highest point being about the middle of the nose and below the superior concha. The stream reaches a lower level during expiration than in inspiration. In order to excite the olfactory cells the odorous particles must, therefore, be carried upwards from the respiratory passages either by diffusion or by eddy currents. In the aforementioned experiment eddy currents were observed both during the inspiratory and expiratory movements. In the living subject it is probable that the ascending currents are more pronounced during inspiration; at this time air movements caused by convection are likely to occur, due to the mixing of the cooler ingoing stream with the warmer air within the nose. But, however produced, whether by convection or simply as a result of the mechanical mixing of the inspired air with that within the nasal passages, eddy currents constitute the main factor

in the stimulation of the olfactory endings, and a sharp inspiration is the most effective means by which such currents are set up. When, for example, we wish to smell some particular scent more acutely we automatically make a sharp inspiration or "sniff." Diffusion is a relatively slow process and is probably of minor importance in bringing the odorous material to the olfactory endings. Even though the nose is filled with odor-laden air we cannot smell while the breath is held. It is during expiration that odorous material liberated from the food as it is masticated and swallowed enter the nose through the posterior nares and ascend to the olfactory area.

It will be recalled that the olfactory hairs are immersed in a layer of fluid secreted by Bowman's glands. The odorous particles must therefore enter into solution before they can come into contact with and stimulate the sense organ. This fact emphasizes again the similarity between the senses of taste and smell. It is probable that odorous materials before they can act as stimulus must also be dissolved in the substance of the olfactory hairs themselves. These structures, since they are stained best by osmic acid, are believed to be composed largely of lipid material. One would expect, therefore, that odorous substances must be soluble in oil as well as in water, and that those which are most freely soluble in both media would be the most potent in arousing an olfactory sensation. This supposition is borne out to some extent by experiment. Ethyl and methyl alcohols, for example, which are freely soluble in water but only slightly in oil, have weak odors as compared with butyl alcohol which dissolves very freely in oil and is also soluble in water. Chloroform, benzol, brombenzol, ether, citral and many other substances with strong odors are soluble in both water and oil. It would appear that high solubility in oil is of more importance for olfactory stimulation than high water solubility; for taking two substances, one with a high solubility in oil but sparingly soluble in water, and the other possessing solubilities of a converse kind, the former has the most powerful odor.

Though it is no longer questioned that the olfactory nerves subserve the sense of smell, some of the earlier investigators (e.g., Magendie) contended that olfaction was a function of the trigeminal nerve. The confusion arose from the fact that certain agents, e.g., ammonia, nitric acid fumes, chlorine, pepper, menthol, peppermint and many others, cause nasal sensations, usually described as pungent, acrid, irritating or cooling.

¹ An electric current acts as an inadequate stimulus. When the nose is filled with normal saline and a constant current passed through the solution an odor which is difficult to describe is experienced upon opening or closing the current.

These are not true olfactory sensations but are due to the stimulation of the trigeminal, which is the nerve mediating chemical sense and common sensibility in the respiratory part of the nasal mucosa. It is often very difficult, however, to dissociate these sensations from smell when the two types of ending are stimulated concurrently. A similar confusion arises, as already mentioned (p. 1049), in the case of taste.

Strong reflex effects, e.g., sneezing, lacrymation, respiratory inhibition, vasomotor reactions, etc., result from irritation of the trigeminal endings, whereas reflexes initiated from the olfactory receptors are as a rule mild in character, and in man are concerned mainly with salivary and gastric secretion. In animals olfactory reflexes play their most important rôle in the reactions of sex and in self preservation—the search for food and protection from enemies. Olfaction is paramount among the senses in its power to awaken a train of associations in consciousness. Everyone is familiar with strange reminiscent aura of past events which is aroused by certain familiar scents (see p. 896).

THRESHOLD STIMULI. Among the most effective olfactory stimuli are *artificial musk, mercaptan, butyric acid, iodoform* and *oil of peppermint*. For example, methyl mercaptan (garlic odor) is perceptible to the average person in a concentration of 1/23,000,000,000 of a milligram per cu. cm. of air. Assuming that 50 cc. of air is required for arousing an olfactory sensation, this would mean that 1/460,000,000 mgm. of the substance is an effective stimulus. The sense of smell is therefore many thousand times (about 1,000 times in the case of ethyl alcohol) more acute than the sense of taste. The minimum perceptible concentrations of various odorous substances are given in the following table.

Substance	Mgm. per liter of air
Ethyl ether.....	5.83
Chloroform	3.30
Pyridine.....	0.032
Oil of peppermint.....	0.024
Iodoform.....	0.018
Butyric acid.....	0.009
Propyl mercaptan.....	0.006
Artificial musk.....	0.00004

(from Allison and Katz)

SENSORY ADAPTATION. The olfactory receptors adapt fairly rapidly. It is a common experience that a disagreeable odor which when first smelt is almost overpowering soon becomes imperceptible. But although lost for one particular odor the sense of smell

is retained for others; the phenomenon therefore is not due to fatigue of the olfactory mechanism,⁴ but is an example of sensory adaptation (p. 806). The rate of adaptation varies for different odors. The receptors become insensitive to oil of orange or to oil of lemon after an exposure of from 2.5 to 11 minutes (average 3 minutes), whereas cumarin (0.2 per cent aqueous solution) cannot be smelt for longer than from 1.75 to 2.3 minutes, and adaptation for the odor of benzoin is more rapid than for that of rubber.

Olfactory adaptation commences to develop from the moment that the odor is first smelt, the threshold rising gradually until complete insensitivity to that particular odor is reached. Even a previous period of exposure to a given odor raises the minimum concentration at which it is perceived for a considerable length of time afterwards. Elsberg found, for example, that the olfactory coefficients (p. 1056) for peppermint, camphor and sassafras were increased to double their normal values if the subject had previously been smelling these substances; and the sensitivity of a person who had been for a time in the operating theater to the odor of ether was below normal several hours later.

CHEMICAL CONSTITUTION IN RELATION TO OLFACTORY STIMULATION. Generally speaking, the olfactory potency of chemical compounds belonging to an homologous series increases progressively from the lowest members of the series to the highest. The odors of the monatomic alcohols, for example, increase in strength from methyl through ethyl, propyl and butyl to amyl; the relative potencies of methyl and amyl alcohols are as 1 to 10,000. Also, compounds which as a group resemble one another in their chemical and physical properties tend to have odors possessing certain common characteristics. For example, the elements sulphur, selenium and tellurium, which belong to the sixth group in Mendeljeff's periodic table, when combined with hydrogen, methyl or ethyl, etc., have strong disagreeable smells. Similarly members of the seventh group, chlorine, bromine and iodine have kindred odors; the odors of chloroform and iodoform, compounds of the first and third elements respectively, are linked together by that of bromoform in which the fragrance of chloroform and the unpleasant odor of iodoform can be detected. Of chemically allied organic substances, ethyl, propyl and butyl acetates have an acetic odor, whereas amyl acetate has not, nevertheless the smell of the lowest of the series is linked with that of the highest through the two intermediate compounds. Thus—

Ethyl acetate, acetic odor

Propyl acetate, acetic odor with slight pineapple flavor

Butyl acetate, slight acetic odor with pineapple flavor

Amyl acetate, no acetic odor, strong pineapple flavor

⁴ Though it is often referred to as such.

Though the foregoing are interesting examples of chemico-olfactory correlation, it is not possible to make anything more than broad generalizations in respect to chemical structure and smell, for compounds which closely resemble one another chemically may have quite different odors and others which show little resemblance in their chemical or physical properties (e.g., hydrocyanic acid and nitrobenzine, garlic and certain arsenical compounds, and artificial and natural musk) may smell very much alike. An attempt has been made in the case of aromatic compounds to relate odor to a particular radical on the benzene ring. Hydroxyl, aldehyde, ketone, ester, nitro and nitril grouping—the so-called *osmophoric groups*—have been suggested as determining the character of the odor; it is believed, however, that the latter is dependent not so much upon which particular radical is present as upon the position which any one of them occupies in the benzene ring.

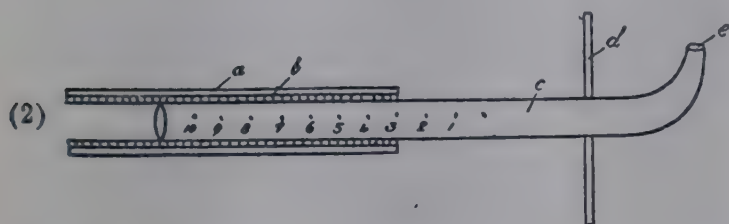


FIG. 496. Diagram of Zwaardemaker's olfactometer. See text.

OLFACTOMETRY. The most widely known method of investigating the sense of smell is that of Zwaardemaker. His olfactometer consists of two tubes sliding one inside the other, as illustrated in figure 496. The inner tube is made of glass and graduated in sections 0.7 cm. long. The outer tube, also of glass, has a lining of indiarubber, beeswax, sealing wax or some other faintly odorous material. The curved end of the inner tube is introduced into a nostril, the opposite one being closed; the subject breathes quietly. The outer tube is gradually withdrawn, thus exposing a greater area of its inner surface to the air current and thereby increasing the concentration of the odorous particles in the inspired air. The highest figure visible on the inner graduated tube when the odor is just perceived indicates the subject's threshold for smell in units termed *olfacties*. This method gives at the best only approximate results, chiefly because the volume of inspired air drawn through the tubing varies considerably from subject to subject and in the same person at different times or even during a single period of observation. In the *blast method* of Elsberg and Levy this factor is controlled. Thirty cubic centimeters of an odorous liquid (e.g., benzene citral, oil of orange, oil of turpentine, butyric

acid, etc.) are placed in the bottle shown in figure 497. The right hand tube is connected to a double nosepiece which fits into the nostrils. By means of a syringe connected to the other tube a measured volume of air is forced from the bottle in one blast at a constant pressure while the subject holds his breath. An equivalent volume of odor-laden air is thus forced into the nose. The volume of the injections is gradually increased in successive blasts until the odor is just perceived and can be named. The smallest volume necessary for identification is called the *minimum identifiable odor* (M. I. O.) or the *olfactory coefficient*.

This method has been employed by Elsberg as an aid in the localization of tumors in the anterior fossa of the skull. In this situation a tumor (e.g., of the



FIG. 497. Illustrating the blast method of olfactometry. (After Elsberg and Levy.)

frontal lobe) is likely, through direct pressure, to involve the olfactory lobe or tract of one or of both sides; or the olfactory nerves may be torn in fractures through the cribriform plate. Unilateral involvement of the olfactory nerves, lobe or tract raises the M.I.O. or completely abolishes the sense of smell on the affected side. A tumor involving both olfactory lobes or tracts will result in lowered acuity of smell or complete anosmia on both sides. Elsberg states that tests for olfactory "fatigue" give valuable localizing aid; the "fatigue" phenomenon is prolonged beyond the normal limits by tumors within the substance of the temporal lobe, but not by those situated extracerebrally (e.g., beneath the frontal lobe). In cases of a generalized increase of intracranial pressure due to other causes the M.I.O. is often lowered.

CLASSIFICATION OF ODORS. The division of odors into categories has proved an extremely difficult problem. There are no basic qualities of olfaction comparable to sweet, salty, sour and bitter tastes. The number of different and distinct smells is legion, and no comprehensive classi-

fication upon the basis of chemical constitution or physical properties can be even attempted. The earliest classification of odors was made by the Swedish botanist Linnaeus (1750). The following one proposed by Zwaardemaker, which is little more than an elaboration of that proposed by Linnaeus, consists of nine categories. It has a purely subjective basis and is therefore of little scientific value.

1. *Ethereal odors*; e.g., of fruits, beeswax, ethers.
2. *Aromatic or resinous odors*; e.g., of camphor, bitter almonds, cloves, lavender.
3. *Fragrant or balsamic odors*; e.g., of flowers, extracted or artificial perfumes.
4. *Ambrosial odors*; e.g., of musk, ambergris.
5. *Garlic odors*; e.g., of garlic, onions and of sulphur and selenium compounds.
6. *Burning odors*; e.g., of burning feathers, tobacco, roasted coffee and meats.
7. *Goat odors*; e.g., caproic acid, sweat and ripe cheese.
8. *Repulsive odors*; e.g., of hyoscyamus and several of the family of the deadly nightshade, bedbug.
9. *Nauseating odors*; e.g., of excrement, decaying meat and vegetable matter.

ACTION POTENTIALS FROM THE OLFATORY PATHWAYS. Gerard and Young have recorded the action currents from the olfactory bulb of the frog. A spontaneous rhythmical discharge occurs in this part of the isolated brain at the rate of about 4 per second. The discharge is taken as representing true automatic activity of the nerve cells of the bulb itself, for the possibility that it was due to the irritation of traumatized structures seems to have been excluded.

In certain fishes (catfish, carp and tench) the olfactory bulb is connected with the forebrain by a nerve strand (the *olfactory stalk*) which measures about 2 cm. long and is composed of from 500 to 1000 medullated fibers. Adrian and Ludwig studied the action potentials in the olfactory stalk of the catfish during stimulation of the olfactory end organs. The latter are contained in a small sac which opens through a nipple upon the surface of the skin above the mouth. Potential changes of small amplitude pass up the stalk as long as the preparation survives, though nothing but distilled water has been introduced into the sac. This *resting discharge* is of very low frequency. When the sac was irrigated with fluid containing small fragments of some odorous material, e.g., putrefying earthworms, a burst of impulses occurred at high frequency after a latent period of from 0.5 to 5 seconds or longer. It was found that the irrigation was more powerfully stimulating if the fluid contained small fragments of the material than if it had been filtered. The nervous discharge is not rhythmical, there being no evidence that groups of fibers discharged synchronously. Mechanical stimulation, caused by pressing upon the roof of the sac or by touching its interior with a brush, was also found effective.

THE QUESTION OF OLFATORY DISCRIMINATION. The great multitude of distinguishable odors brings up a question for which no answer is forthcoming, namely, "What is the mechanism underlying olfactory differentiation?" "How do we detect the difference between two scents such as those of the violet and the rose?" Or, to make the question still more difficult, "How does a dog recognize the smell of his master among the smells of other persons?" Were there a limited number of basic odors, as there are fundamental tastes, the problem would not be difficult, but such are unknown. For vision we can postulate three types of receptor, each responsive to a particular set of wave lengths, and each discharging impulses along a specific nerve fiber to the brain (see doctrine of specific nerve energies (p. 808). A place theory (p. 1041) is capable of accounting for pitch discrimination, and four functionally distinct types of taste bud, each with its specific nerve fiber, for the perception of the fundamental sensations of taste. But it is not conceivably possible that every one of the immense number of different odors is subserved by a specific type of end organ with its own nerve fiber. Furthermore, new and distinct odors are being created in industry every day. From what we know of other senses we can presume that the *intensity* of the olfactory sensation is related to the frequency of the impulses discharged to the olfactory center. This is borne out by the experiments of Adrian and Ludwig just described. But no satisfactory theory has been proposed to explain the different qualities of the olfactory sense.

THE EFFECT OF ONE ODOR UPON THE PERCEPTION OF ANOTHER. Strong odors tend to mask weaker ones. If two scents are of about equal strength a blend of the two is smelt or both are identified; but if one is considerably stronger than the other it alone, as a rule, is smelt. On the other hand, certain pairs of odors in appropriate relative concentrations are antagonistic, and when the two are sniffed together both are diminished. Iodoform, for example, is antagonized by balsam of Peru, musk by bitter almonds and ammonia by acetic acid. Other pairs of neutralizing odors are cedarwood and rubber, beeswax and balsam of Tolu, benzoin and rubber, and camphor and eau de Cologne. Though the neutralizing effect may in some cases be simply chemical or physical in nature, in others there seems to be a true physiological antagonism, for the phenomenon is observed when mixing is avoided by leading the two odors directly one to each nostril.

ANOMALIES OF OLFACTION. Loss of the sense of smell or *anosmia* is not infrequent as a temporary condition, e.g., as a result of inflammation of the nasal mucosa or of the local application of cocaine or adrenaline. Complete and permanent anosmia is rare in otherwise normal persons and is usually due to absence of the olfactory bulb or olfactory nerves, but bilateral or unilateral olfactory deficiencies are frequently associated with lesions in the region of the olfactory lobes (p. 1052). Albinos are said to be anosmic, which suggests that the pigment in the supporting cells of the olfactory epithelium, which possibly serves an essential function, is lacking. Inability to smell certain odors is not uncommon. Some persons, for example, cannot smell hydrocyanic acid; the odor of mignonette, benzoin, methyl alcohol or vanillin cannot be smelt by others. Even such a strong, disagreeable smell as that of a rotten egg or of feces, may not be sensed. Partial anosmia for all scents may result from excessive smoking. *Hyperosmia* is not unusual in hysteria, in certain cerebral diseases, in raised intracranial pressure and during the initial stage of the action of cocaine. Olfactory hallucinations may occur in lesions of the temporal lobe (p. 896). In cerebral tumors, especially of the frontal or temporal lobes, an odorous material introduced into one nostril may be referred to the other. This phenomenon, known as *olfactory alloesthesia*, is analogous to *allocheiria* mentioned on page 800.

COMMON CHEMICAL SENSE

The general body surface of fishes and many other aquatic forms is sensitive to various types of chemical irritant, as are also the moist skins of amphibians. The elicitation of reflex responses from the foot of a pithed frog stimulated by a weak solution of sulphuric acid is a well known laboratory exercise. In man the common chemical sense is restricted to surfaces which are kept constantly moist, namely, the buccal and nasal mucous membranes, the conjunctivae and the mucosa of the anal canal. The common chemical sense of the first three is subserved by the trigeminal nerve, that of the anal canal by the pudendal nerve. It has already been pointed out (p. 1049 and p. 1054) that the sense organs subserving this sense in the mouth and nose are distinct from the gustatory and olfactory endings, and apparently they are not identical with those subserving pain, for dissociation of chemical and pain sensations can be effected by cocaine, the latter being abolished before the former. Thus, after the application of a 1 per cent solution of the anesthetic to the foot of the frog no response is given to pinching, pricking or scratching, while reactions to chemical agents can for a time be elicited.

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CHAPTER XXVIII

SPECIAL FEATURES OF THE CIRCULATION IN DIFFERENT REGIONS

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SECTION III

CHAPTER XXIX

THE MECHANICS OF RESPIRATION

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SECTION VI

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CHAPTER LXI

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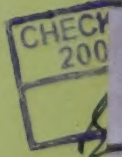
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